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VOLUME XXII NUMBER 6

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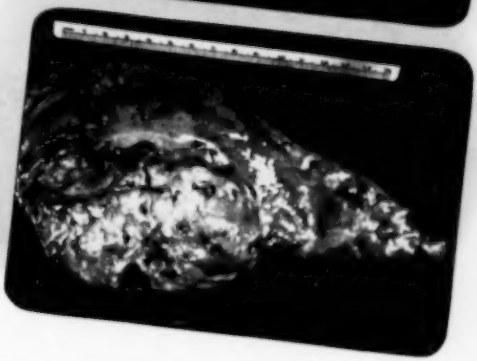

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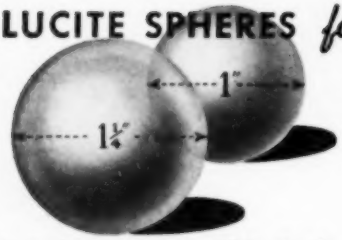

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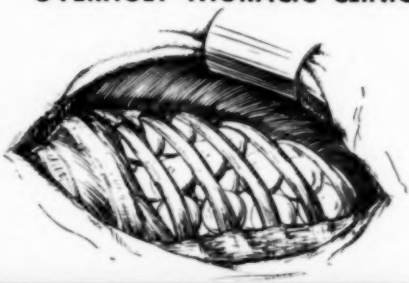

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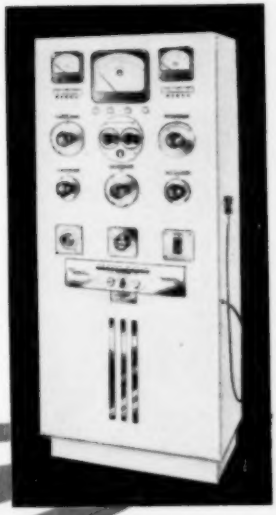

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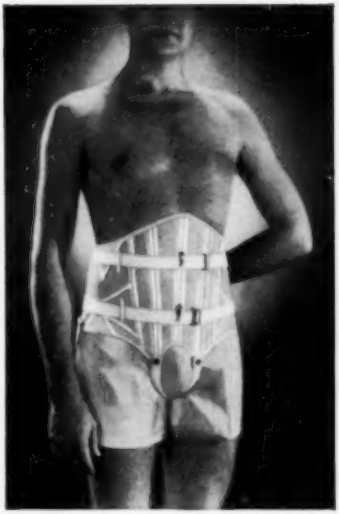

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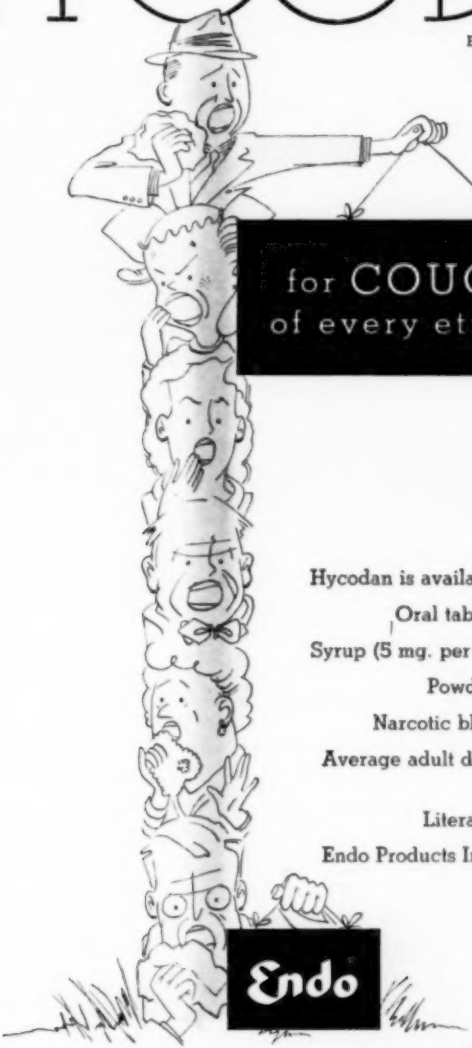

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(For more information about 'Neo-Penil', see page 26)

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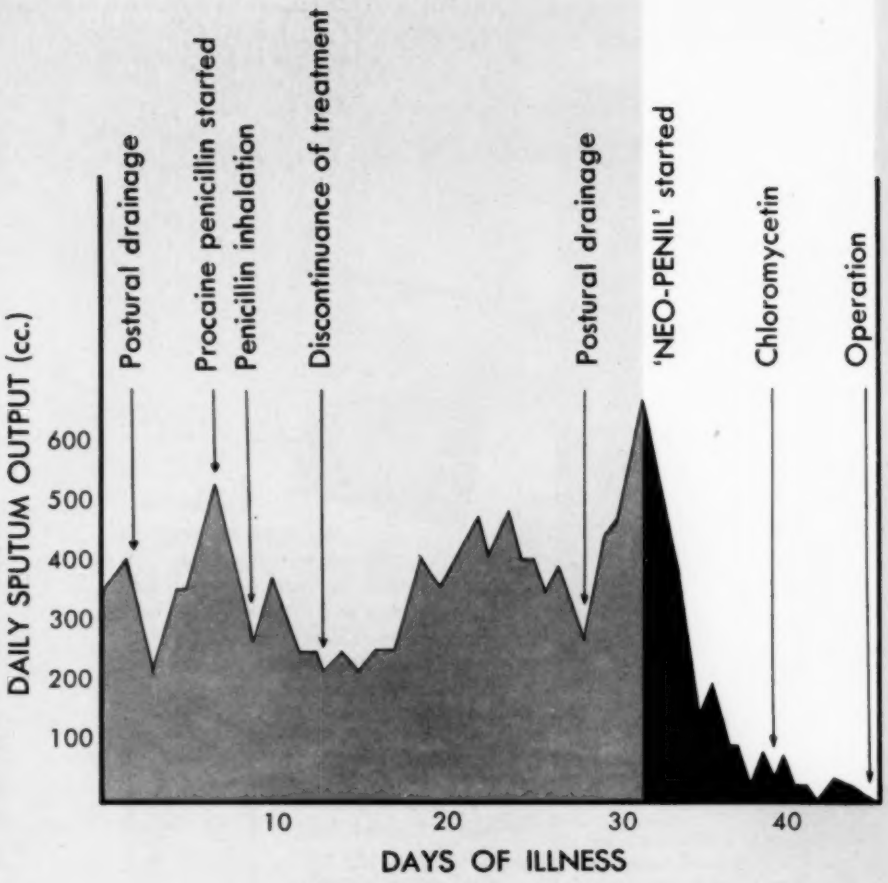

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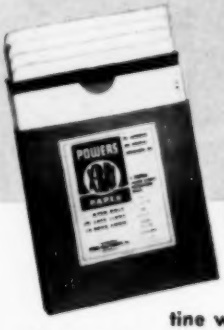

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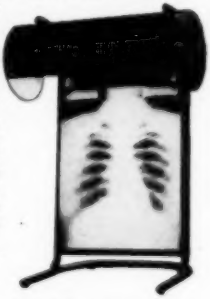

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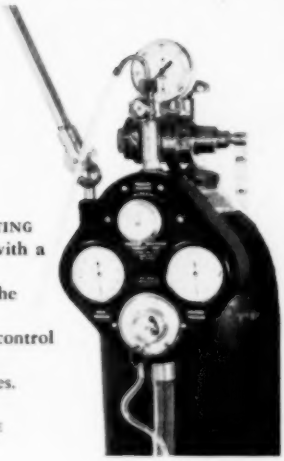

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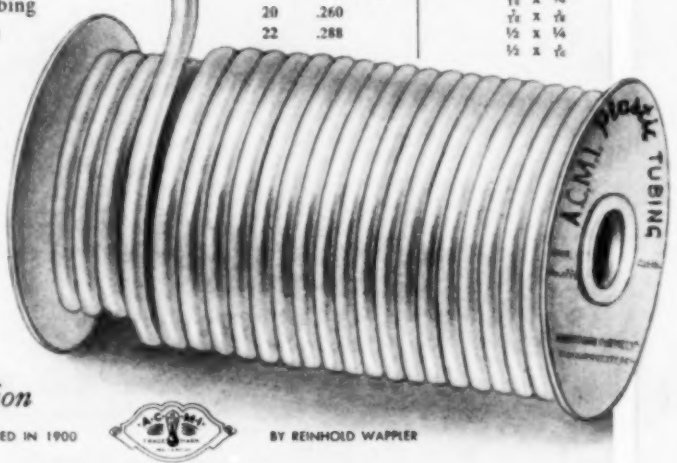

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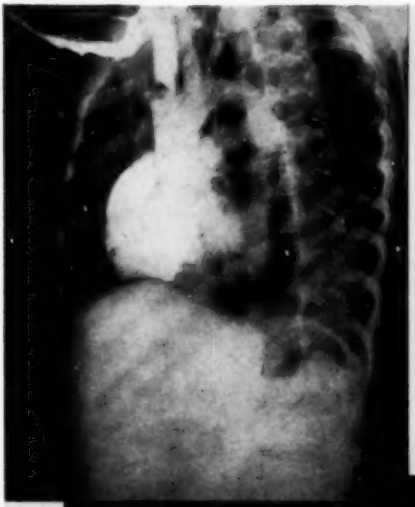

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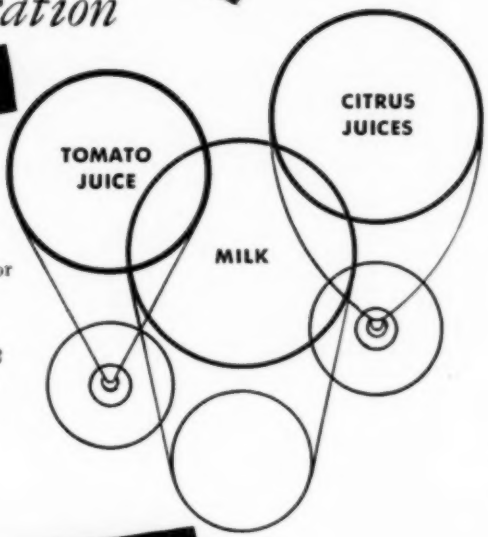

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1. Ansbro, F. P., and others: Anesthesiology *13*:306, 1952. 2. Jason, A. H., and Shattel, H. E.: Postoperative Pain Control, presented before the Section on Anesthesiology of the American Medical Association, Chicago, Ill., June 10, 1952. 3. Deaton, W. R., Jr., and Bradshaw, H. H.: Am. Surgeon *18*:616, 1952. 4. Puderbach, W. J., and others: Journal Lancet *72*:203, 1952. 5. Tucker, C. C.: J. Kansas M. Soc. *53*:230, 1952. 6. Gross, J. M., and others: New York State J. Med. *52*:1413 (June 1) 1952. 7. Penn, S. E.: Arch. Otolaryng. *56*:59, 1952. 8. Cappe, B. E., and Pollin, I. M.: Am. Pract. & Digest Treat. *3*:739, 1952.

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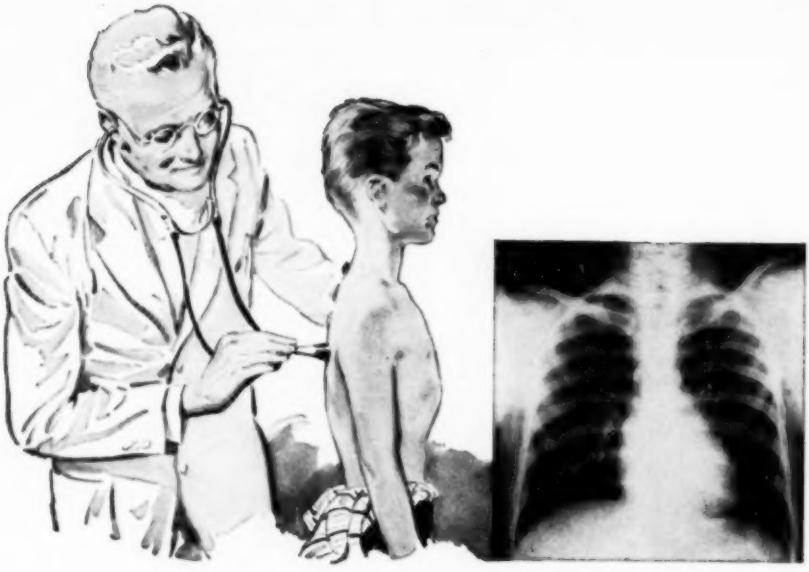

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1. Segal, M. S.: Dis. of Chest 14:795-823, 1948.

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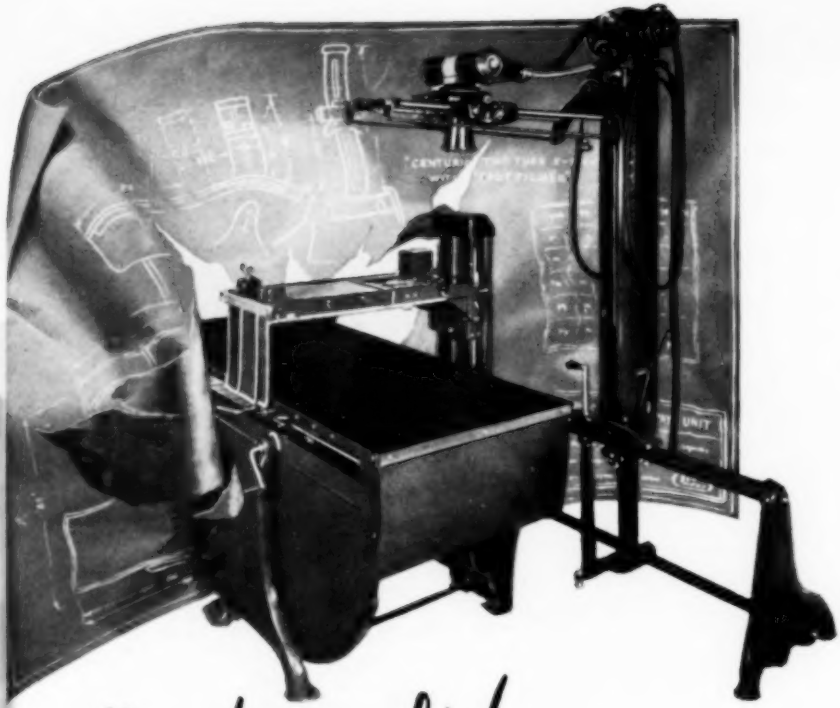

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DISEASES *of the* CHEST

VOLUME XXII DECEMBER 1952 NUMBER 6

The Effects of the Diminished Incidence of Primary Infection on the Tuberculosis Control Program*

J. ARTHUR MYERS, M.D., F.C.C.P.
Minneapolis, Minnesota

Primary infection is the starting point of all tuberculous lesions. Without the initial invasion of tubercle bacilli there can be no illness or death from tuberculosis. Efforts to control this disease in many places has been limited largely to the sick and dying, and more recently in a small way to those not yet ill or seriously so, but who have x-ray shadow-casting lesions. So much time was consumed on these phases of tuberculosis that little or no consideration was given to the control of primary infection. Thus the fountainhead continued. The presence of gross lesions or a considerable degree of ill health had to exist before an attack was made on the tubercle bacillus. Usually in cases so found, the disease already was contagious and tubercle bacilli had been passed on to the bodies of persons and animals associated with the hosts. Moreover, the majority of hosts were already destined to long periods of invalidism, and many to untimely death. Most of these persons had passed through long periods—months, years and even decades, in apparently good health, but with primary infections in their bodies for which nothing had been done. Indeed, primary infections were so encouraged and coddled that they were the safest possible haven for tubercle bacilli. They were thought to be universal in young adulthood and all subsequent ages throughout the civilized world.

Prior to 1890, primary infections were usually detected only at necropsy. In some parts of the world the bodies of practically all adults and most children dead from any cause revealed them.

*Presented at the Seventeenth Annual Meeting of the American College of Chest Physicians, Atlantic City, New Jersey, June 8, 1951.

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After 1890 the reaction to tuberculin manifested their presence during life. In many places where tuberculin testing was done, reactions began to appear among young children and the incidence rapidly increased to include the majority of young adults. Thus it was assumed that all persons in older adult life carried primary infections. These were regarded almost as much a part of adult human bodies as the various organs with which they were born. The occasional young adult who did not have primary tuberculous infection was looked upon as an abnormal person and was considered in great danger of developing galloping consumption.

In a few places, particularly the United States, groups of physicians, small at first, became convinced that all tuberculous infections should be prevented. Notable in this contention was E. L. Trudeau, who emphasized the importance of protecting children against contagion. A sanatorium building program was soon under way whose main purpose was to prevent persons with contagious tuberculosis from spreading tubercle bacilli to children, other members of their households and their community associates.

One of the most effective health education programs in history was begun by the National Tuberculosis Association in 1904 and has increased in scope and intensity to this moment. Numerous other organizations, national and local as well as the practicing medical profession, joined in the campaign to stop the dissemination of tubercle bacilli.

The establishment of a Division of Tuberculosis in the United States Public Health Service in 1944, with its subsequent promotion of mass x-ray surveys in our most densely populated areas, has brought to light many persons with previously unknown tuberculosis. The finding of such cases and providing proper isolation and treatment has been an important factor in protecting the public against primary tuberculous infection.

The veterinary profession has long recognized primary tuberculous infection in animals, particularly cattle, as an ill omen. They knew that every animal so infected as manifested by the tuberculin reaction was a potential reservoir of tubercle bacilli from which dissemination might occur among other animals and people. Therefore, they set up an eradication program in 1917 which consisted of removing from the herds of the United States all animals which had contagious tuberculosis as well as those which at the moment presented no evidence except the tuberculin reaction. One of the main purposes of this program was to protect animals and people from primary and secondary invasions with bovine type of tubercle bacilli.

Opposition to Preventive Measures

Strange as it may seem, early attempts to protect people and animals against primary infections with both bovine and human types of tubercle bacilli were strenuously opposed. Some persons contended that the problem was of such magnitude that it would be impossible to provide funds to build and maintain sufficient sanatoriums for contagious people and to reimburse owners for the large number of cattle that would be sacrificed. A more potent objection was that children would be denied tubercle bacilli which were believed to be essential to immunize them against clinical disease in adulthood.

Veterinarians were told that if they eradicated tubercle bacilli from the cattle herds of America they would bring on generations of cattle of so-called virgin soil; that is, if such cattle should at some subsequent time become infected with tubercle bacilli they would have no resistance and tuberculosis would become epidemic among them.

Progress Continued with Phenomenal Accomplishments

The opposition was sufficiently overcome that sanatorium building and other methods of protecting the population against first infection with human type of tubercle bacilli proceeded. By 1947 there were 830 institutions with 120,496 beds for tuberculosis in Continental United States. These included 21,317 beds in hospitals for the mentally ill and penal institutions.

In the United States mortality rates fell to almost unbelievable levels. Among infants from birth to one year, the mortality rate was 168.6 per 100,000 in 1915, but only 10 in 1948—a decrease of 94.07 per cent (Table I). During the same time, among children from one to four years the mortality rate decreased 89.85 per cent. The decrease was 92.19 per cent among children from five to 14 years, and 88.23 among young adults from 15 to 24 years (Table I).

TABLE I

TUBERCULOSIS MORTALITY RATES, UNITED STATES, 1915 THROUGH 1948

	1915	1948	Per cent Decrease
Birth to 1 year	168.6	10.0	94.07
1 to 4 years	68.0	6.9	89.85
5 to 14 years	26.9	2.1	92.19
15 to 24 years	146.1	17.2	88.23

The tuberculosis mortality rate for people of all ages dropped from 146 in 1915 to 22.2 in 1950 and to about 20 in 1951.

In New York, the world's largest city, the number of deaths among children under 15 years of age fell from 1200 in 1915 to 74 in 1948, a decrease of 93.83 per cent. In the State of Minnesota, among children under 15 years of age the tuberculosis mortality rate was 34.1 per 100,000 for the five year period, 1915-19. In 1949, it was 1.3 per 100,000, a decrease of 96.2 per cent. Among infants under one year of age, the rate was 130 per 100,000 in 1915-19, but only 4.4 in 1949, a decrease of 96.6 per cent. The rate among persons of all ages was 102.2 in 1915 and 8.6 in 1950, a decrease of 91.6 per cent.

Veterinarians and their allies were frequently retarded by litigation, etc., but they pressed forward with a tuberculosis eradication program, which began in 1917. That year, at the points of federal inspection 40,746 cattle were condemned as inedible because of tuberculosis. In 1951, only 569 animals were so condemned, a decrease of 98.6 per cent. In 1916, one year before the nationwide eradication program began, enough cattle were condemned by federal inspectors to make a 15-mile solid trainload of live cattle. In 1951, such animals could be accommodated in a train less than 0.3 miles long.

From 1917 to 1950, 322,474,607 tuberculin tests were administered to cattle of this country and the 3,978,763 reactors were slaughtered. The veterinarian's accomplishment has been phenomenal. By 1951 he had reduced the incidence of tuberculous infection among the cattle of America to 0.14 per cent. There is some evidence to indicate that a considerable percentage of the relatively few animals which become infected annually receive their tubercle bacilli from human associates rather than from other cattle. There are large areas in this country where no animal can be found with even primary tuberculosis (tuberculous infection).

Veterinarians have also done much to prevent primary tuberculous infection among people by controlling tuberculosis among other domestic animals and pets such as dogs, cats and parrots. Their program has been so successful that a large number of people have been protected against primary tuberculous infections. Wherever tuberculosis has been controlled among cattle there has followed definite decrease in infection attack rates, mortality and morbidity among the people of the same areas.

Since tubercle bacilli of the human and bovine types are transmissible from animals to people and from humans to animals, it is futile to attempt to control the diseases in people without controlling it in animals and vice versa.

The veterinarians' program combined with the sanatorium move-

ment has in just a few decades almost reversed the situation with reference to primary infections among people. Early in the 20th century it was said that in many places in this country 90 to 95 per cent of young adults had primary infection. Now, on the basis of actual testing we know that in large parts of the country 90 to 95 per cent of young adults have been protected against such infection. As one descends the age scale, large numbers of grade schools are found in which only 2 or 3 per cent of the children have primary infections, and there is a rapidly mounting number of such schools in which no child has been infected. In these same areas pre-school children who react to tuberculin have become rare. Starting again from young adult life and ascending the age scale, one finds in these same areas a high percentage of persons in the ages of 20 to 30, and even 40, who do not react to tuberculin. In some rural counties testing of adults of all ages has revealed that less than 25 per cent have primary tuberculous infection.

In the United States primary infections now occur more often among adults than among children. In many areas the annual infection attack rate in both childhood and adulthood is well under 1 per cent. Since so much of life's span is spent in adulthood, there are many more years during which primary infection may occur. Since the defense mechanism of the human body is as effective against the first invasion with tubercle bacilli in adulthood as in childhood, and since everyone becomes a potential case of tuberculosis immediately after the first invasion with tubercle bacilli, it is obvious that the longer primary infection can be postponed the less likelihood there is of the individual falling ill or dying from tuberculosis.

Theories Replaced by Facts

As the program of tuberculosis control among people and animals progressed, theories which had so retarded progress were replaced by facts. For example, the theory that the bovine type of tubercle bacillus has low virulence for human tissues was proved to be erroneous. Indeed, it was found capable of producing just as disabling and killing disease among people as the human type. In countries which have not controlled tuberculosis among the cattle herds, the bovine type of tubercle bacillus continues to wreck havoc among children and young adults, causing 50 per cent or more of all cases of tuberculosis of the skin and peripheral lymph nodes, 20 per cent of tuberculous lesions of bones, joints and genito-urinary organs, 25 per cent of fatal tuberculous meningitis and miliary disease, and 1 to 6 per cent of the cases of pulmonary tuberculosis. Such facts completely squelched the theory that the

bovine type of tubercle bacillus should be preserved to immunize children. It was obvious that to provide children with bovine type of tubercle bacilli in their food to produce so-called immunity caused too much illness, deformity and death to justify the practice even if the bovine type of tubercle bacillus had been proved to have some immunizing power.

As it became obvious that children were so protected against primary infection that a preponderance of them were entering adulthood without tubercle bacilli in their bodies, there was still a belief that every human body should contain tubercle bacilli and it was actually recommended that living germs of reduced virulence be administered to every child. Time has shown that where this has been done, the tuberculosis problem has not been solved as well as in areas where children have been protected against tubercle bacilli of all types and all degrees of virulence.

The creation of "virgin soil" theory was also found untenable. This was based on the opinion that if people and animals were deprived of tubercle bacilli, generations would develop with no immunity (virgin soil) and should they then become infected they would be decimated. Veterinarians showed that when animals whose ancestors have been free from tubercle bacilli for generations become infected with tubercle bacilli, their defense mechanism operates in precisely the same manner as that of animals whose ancestors have been tuberculous for many generations.

As late as 1949, a physician wrote: "The situation in Minnesota may be likened to a safety zone that lies in the midst of streaming traffic. To carry the analogy a bit farther, the wise Minnesotan will remain on his little island if he wishes to retain his health. To travel abroad without any immunity might prove particularly hazardous. Of course, if he so desired, he might remain where he is until traffic around him quieted down, but that might take a good many more years." The writer of this article apparently did not know that in nine other states tuberculosis was at lower ebb than in Minnesota. Therefore there were 10 safety zones or islands and a sizable number of others in this country with tuberculosis at almost as low ebb. This author apparently did not know that Minnesotans travel as freely in other parts of this nation and abroad as citizens of other states. Yet their tuberculosis mortality, morbidity and infection attack rates continue to decrease. Moreover, large numbers of young women and men served in countries where tuberculosis is rife during World War II, and many became infected with tubercle bacilli. In fact, the incidence of tuberculin reactors among entering university students was 6.4 per cent in 1945, but in 1946 when large numbers of those who had

been abroad in service entered school, the incidence of tuberculin reactors was 19.3 per cent. These individuals who had been protected against tubercle bacilli through their lives but became infected while abroad, presented no different tuberculosis problem than that seen among students some years before, when 19 per cent or more reacted to tuberculin. After 1946, as the number of veteran students decreased there were fewer tuberculin reactors on entrance, reaching 11.2 per cent in the school year 1948-49.

We have observed a large number of young adults, principally students of nursing and medicine, who developed primary tuberculous infection. Among them, no different kinds of clinical disease were found and no greater number developed this disease subsequently than among those infected as children.

Therefore, the theory that it is dangerous to the future control of tuberculosis to prevent the young from becoming infected with tubercle bacilli has been replaced with the fact that the only safe procedure is to protect humanity everywhere, regardless of age of individuals, against primary infection and reinfection with tubercle bacilli. The idea, that bringing on generations of people uninfected with tubercle bacilli creates a dangerous so-called virgin soil, is a myth. The old theory that the child or adult who has tuberculous infection as manifested by sensitivity to tuberculin walks in a charmed circle of safety, has been replaced by the fact that such persons walk within the circle where all illness and death from tuberculosis occur.

The program early adopted by the National Tuberculosis Association and practically every health organization, including the United States Bureau of Animal Industry, designed to prevent first infection with tubercle bacilli has proved to be the only method by which the disease can be adequately controlled and ultimately eradicated.

The Leprosy Example

Centuries ago a strikingly similar method was employed successfully in the control and eradication of leprosy. This disease had long been the scourge of mankind. It was present in Palestine throughout the period of the writing of the Old and the New Testaments. It was the common chronic disease in Western Europe in the 13th and 14th centuries. Long before Hansen discovered the bacillus of leprosy (1874), its contagiousness was recognized. It became obvious that the only method by which it could be controlled was to isolate all lepers. This was undertaken on a tremendous scale. In Western Europe alone, 20,000 or more, and in England, 200 or more leprosariums were provided for the isolation

of lepers in order to protect the public against contagion. Since most lepers had lesions on exposed parts of their bodies such as the hands and face, diagnosis was a simple procedure. Thus, practically all lepers were detected and isolated. By this method leprosy was eradicated from England and most of Western Europe by the end of the 16th century.

Similar control and eradication of tuberculosis was long handicapped because most persons with contagious disease had no visible manifestation on the exposed surfaces of their bodies. Lesions were in internal organs, especially the lungs. Only within the present century has it become possible to detect all persons harboring tubercle bacilli. Those with macroscopic lesions in the lungs are usually found by the x-ray shadows they cast. Not all shadow-casting lesions are tuberculous, and not all tuberculous lesions found are contagious. However, our differential diagnostic armamentarium enables us to determine in most cases which shadow-casting lesions are tuberculous and also which of them are progressive and contagious.

Most persons who have tuberculosis at any given time do not have shadow-casting lesions; however, their disease is readily detected by the tuberculin reaction. It is well known that every characteristic tuberculin reactor is a potential case of clinical tuberculosis. Those in whom the disease is destined to evolve to clinical proportions when examined periodically usually have their lesions detected before they cause illness or become contagious. The efficacy of our methods of isolation and treatment has been proved beyond doubt.

Although more effort is required to find tubercle bacilli in human bodies than to diagnose leprosy by superficial skin lesions, they can practically all be found with considerable promptness. In fact, we now have the advantage over those who controlled leprosy in being able to find persons who have tubercle bacilli in their bodies before clinical lesions appear.

Thus, centuries after leprosy was eradicated from England and most of Western Europe, a tremendous tuberculosis problem exists in many parts of the world which can now be eradicated by essentially the same methods as were employed in leprosy.

David T. Smith has pointed out that our European ancestors of the Middle Ages did a thorough and efficient job in the control of leprosy and set up standards which we, with all our modern advantages, have not equaled for tuberculosis. He states that every individual with active tuberculosis must be detected, isolated and treated until he is no longer infectious, as this constitutes the only sure way to eliminate tuberculosis.

Vantage Ground Acquired

The diminished incidence of primary tuberculous infection in this country has placed tuberculosis workers on the most secure ventage ground of all time. It has brought tuberculosis into bold relief so the most refined armamentarium is applicable. In some areas the incidence of primary infection has been so low that refined methods have been employed for a quarter of a century, during which their efficacy has been thoroughly established. These refined methods begin with the pre-infection stage, and the first step consists of detection of the presence of tubercle bacilli at the earliest possible moment among those who become infected. This is attainable only by the tuberculin reaction, which is dependent upon the establishment of sensitivity to tuberculoprotein in the individual's tissues.

Within an hour after tubercle bacilli invade the body, they are focalized in various points and lesions begin to form. These lesions are microscopic and can be found by no phase of the examination of the living body for several weeks (three to seven). At the end of this time allergy has usually reached such a degree that its presence is readily detected by the tuberculin reaction. At this time no other phase of the examination reveals the presence of tuberculosis in more than an exceedingly small percentage of those who have it. There are no external manifestations indicating illness or abnormal physical signs by the conventional examination. X-ray shadow-casting lesions may be seen in five to eight of each hundred who have just become reactors to tuberculin. The chests of the other 92 to 95 per cent are entirely clear on x-ray inspection because (a) the lesions are too small or not dense enough to be revealed by this macroscopic method. (b) They are obscured from view by the shadows of other organs such as the heart and diaphragm, which amounts to about 25 per cent of the lungs. (c) They may be extrathoracically located. Nevertheless, the tuberculin reaction indicates the presence of allergy and of tubercle bacilli, both of which are prerequisites for the development of clinical tuberculosis.

The tuberculin test is the radar of tuberculosis. With uncanny accuracy it locates the persons and animals quickly and inexpensively who have primary lesions containing tubercle bacilli in their bodies. A long step was taken when Koch isolated the tubercle bacillus. This afforded one of our only two specific findings in the diagnosis of tuberculosis. However, it was soon learned that the great majority of persons who have tuberculous lesions in their bodies at any given time do not eliminate tubercle bacilli. Usually it is only those in whom gross lesions develop and often after great destruction has occurred that tubercle bacilli can be found

in the secreta, excreta, bone marrow, spinal fluid, pleural fluid, etc. By the time tubercle bacilli can be found in sputum, the disease is already contagious and usually in an advanced stage.

Although sensitivity to tuberculoprotein is the indispensable ally of the tubercle bacillus in causing destructive disease, man learned how to detect its presence by the simple and harmless tuberculin reaction. He then learned that every person and animal presenting a characteristic tuberculin reaction has tuberculous lesions containing tubercle bacilli. Thus, without actually seeing tubercle bacilli through the microscope one accurately determines their presence by the reaction to tuberculin.

Knowing that tubercle bacilli are in a human body, one also has gained the information that a contagious case of tuberculosis has been in contact with that person. Examination of contacts of tuberculin reactors often reveals unsuspected contagious cases of tuberculosis. The tuberculin test when properly used is our best epidemiological agent.

It is only by the tuberculin reaction that one is able to determine quickly and accurately the effectiveness of a tuberculosis eradication project. This is accomplished by periodically testing children born since the program began and comparing the incidence of reactors in the same age groups which obtained prior to the project.

As yet we have no way to determine which persons who develop primary infections will have clinical lesions evolve; therefore, all tuberculin reactors must be kept under close surveillance in order to detect lesions which attain gross proportions as soon as possible. The best method of finding these evolving lesions in the lungs is by periodic x-ray inspections of the chests of tuberculin reactors. In vast areas of the United States the number of reactors to tuberculin has become so small that it is physically possible to find all of them and inspect their chests frequently by x-ray films. Periodic examinations of these tuberculin reactors should be complete. They should always include but never be limited to x-ray inspection of the chest because of the possibility of the development of extrathoracic lesions.

When x-ray shadow-casting lesions appear they must be carefully investigated with reference to etiology. Those persons proved to have progressive tuberculosis should be treated and those who are eliminating tubercle bacilli through the sputum should be under strict contagious disease technique.

Eradication Attainable Through Persistent and Prolonged Effort

As the incidence of primary tuberculous infection decreases, our vantage ground improves. We have the advantage of the veter-

inarians' experience and accomplishment with large areas of the United States where the tubercle bacillus has been eradicated from the cattle herds and with an extremely small amount of tuberculosis among cattle of the entire nation. This country no longer has to expend vast sums of money in reimbursing owners of cattle for those condemned to rendering tanks. Funds are now being spent more profitably to test and retest animals periodically and thus find a high percentage of those that have become infected before the disease is contagious and when little loss is suffered by the owners.

Among humans, to a great extent caring for the ill and dying will gradually be obviated and thus money and personnel can be transferred to more refined activities. Chronic pulmonary lesions that are detected as soon as possible after they start to evolve require much shorter periods of treatment than those of long duration and many of them do not need hospitalization. Most of them can be prevented from becoming contagious and thus the tubercle bacillus can not perpetuate itself in other human and animal bodies.

Despite the rapid decrease in the incidence of primary tuberculous infection there are still in most communities a sizable number of persons who have already acquired such infections, many of which occurred before the present excellent tuberculosis control program was well under way. These must be found and watched.

Since 1940 our tuberculosis problem has been increased by persons who acquired primary infection elsewhere. During World War II and immediately thereafter, approximately 15 million of our citizens in military service were sent to nations where much contagious tuberculosis still exists. No one knows the exact number, but many developed primary tuberculous infections before discharge from military service. In South Korea, before the present war the tuberculosis mortality rate was reported as 1000 per 100,000. Obviously many of our citizens stationed there have and are acquiring primary infections. This also applies to some degree to those who in recent years have been stationed in other parts of the world where tuberculosis is still prevalent.

In the past few years several hundred thousand displaced persons have been located in the United States. For the most part they had spent their lives in countries where approximately all adults have primary tuberculous infection; therefore it is assumed that practically all displaced persons have such infections. They must be located and kept under close observation as many of them are sure to develop clinical tuberculosis.

It has been estimated that from 3,000,000 to 5,000,000 aliens

have entered this country illegally. They are said to be from countries where tuberculous infection is well nigh universal among adults. As yet, there appears to be no way to locate them for periodic examination. It seems unlikely that those who develop clinical tuberculosis will seek care until totally incapacitated. Thus they will disseminate tubercle bacilli among their associates.

It has long been known that primary tuberculous infections "burn out." How often this occurs has not been determined. Recent observations suggest that all bacilli die in lesions of primary infections more often than was formerly believed. However, it seems doubtful that this number would offset the primary infections this country has acquired through military personnel, displaced persons and illegal aliens.

In most communities there is enough refined work to keep all tuberculosis societies, other organizations and the medical profession busy considerably beyond the lifetime of anyone now engaged in the tuberculosis eradication program. It is unfortunate that officials of many tuberculosis organizations apparently believe their job is about done and therefore they should engage in other endeavors. There is not a tuberculosis organization in this country that has completed the first half of its job. To base conclusions on mortality and morbidity rates or the number of persons found with gross lesions, not yet ill, is false. It is the number of persons in each community whose bodies contain primary tuberculous infection that constitute the only accurate criterion of the tuberculosis problem of the future.

Wherever the incidence of primary infection is high, one finds correspondingly high morbidity and mortality rates. In nations where primary infection is universal among adults, one-fourth to one-third of deaths from all causes are due to tuberculosis. On the other hand, wherever the incidence of primary infection has been reduced there has occurred a decrease in morbidity and mortality rates. In the United States, in 1948, of all causes of death tuberculosis was responsible for only 2.4 per cent among the white and 7.1 per cent among the Negro population. In some of the states where special effort has been made to prevent primary infections the percentage of deaths from tuberculosis has markedly decreased. In 1910, among deaths from all causes in Minnesota 10 per cent were due to tuberculosis, whereas in 1950, it was only 1.17 per cent. In this state the morbidity rate has so decreased that some of the smaller sanatoriums have been closed.

Eradication of primary infection must be our goal. There are a good many entire counties in the United States at this moment, any one of which by adequate support could within a reasonable period of time have the recognition of being the first area of its

kind in the world to have exterminated the tubercle bacillus.

Now that the number of persons whose bodies contain tubercle bacilli has so markedly decreased; the presence of these primary infections can be determined within less than two months after the invasion of tubercle bacilli; those with such infections who are destined to develop chronic reinfection type of pulmonary disease can usually have such lesions detected on an average of two and one-half years before they cause illness or become contagious; and since such lesions can usually be treated successfully, the stage is set for reducing the incidence of primary tuberculosis to the vanishing point.

SUMMARY

1) Primary tuberculous infection is the fountainhead of all tuberculosis.

2) Most attempts to control this disease have been directed against gross lesions while primary infections were unmolested and even encouraged.

3) Early in the 20th century in the United States a small group of physicians began to advocate protection of children from primary infections.

4) This was strenuously opposed on the ground that such infections protect against subsequent clinical disease.

5) The opposition was partially overcome and sanatoriums were built for the isolation of persons with contagious disease. A nationwide educational campaign was instituted. Veterinarians organized a national tuberculosis eradication program which was a potent factor in preventing primary infection in people and animals.

6) Accomplishments were phenomenal. Mortality rates for all ages in the United States decreased 82 per cent between 1915 and 1949, and 94 per cent among infants during the same period. In New York City, among children under 15 years old the mortality rate decreased approximately 94 per cent between 1915 and 1948. The primary infection attack rate tumbled to less than 1 per cent per annum in many places, a small fraction of 1 per cent in others, and primary infections disappeared among children of many entire schools.

Condemnation of carcasses of cattle to rendering tanks decreased 98.6 per cent between 1917 and 1951. By 1951 the incidence of tuberculous infection among cattle had decreased to 0.14 per cent. In large areas primary infection has been eradicated from cattle.

7) As the work progressed, erroneous theories were replaced by facts, as follows: (1) The bovine type of tubercle bacillus long thought to be of low virulence for man produces as incapacitating and killing disease in people as the human type of bacillus. (2) The

bovine type of bacillus, as it occurred in dairy products so highly recommended to protect children against later clinical disease, was found not only unsafe, but possesses no dependable immunizing quality. (3) Protecting people and animals from primary infections would create "virgin soil" for later attacks of tuberculosis was found to have no factual basis. Both people and animals respond to primary infection in adulthood as they do in the early years of life.

8) The diminished incidence of primary infection has afforded the opponents of tuberculosis the best ventage ground of all time. The tubercle bacillus has been brought into bold relief where it can be attacked directly by refined methods.

9) This situation permits extensive use of the tuberculin test by which the presence of primary infection can be detected within two months after the invasion with tubercle bacilli occurs. Periodic x-ray film inspection of chests of tuberculin reactors locates chronic reinfection type of pulmonary lesions on an average of two and one-half years before they cause symptoms and usually before they liberate tubercle bacilli. Lesions found in this stage of evolution can usually be successfully treated in much less time than those which have become more advanced and are contagious.

10) This method has been in use sufficiently long and in large enough areas to establish its efficacy. It is the only method known today by which tuberculosis can be eradicated.

11) By isolating lepers in leprosariums to protect the public against contagion leprosy was eradicated from England and most of Western Europe by the end of the 16th century. Eradication of tuberculosis can be accomplished as it was in leprosy by preventing primary infections from developing in uninfected people and animals. Such infections have already been prevented in a large segment of our human and animal population. Continuation of the present methods is adequate. Eradication of tuberculosis in any community or nation can be announced, not when people and animals stop falling ill and dying, but when primary infections have vanished.

RESUMEN

1) La infección primaria tuberculosa es el venero de toda tuberculosis.

2) La mayoría de los intentos de dominio de esta enfermedad se han dirigido contra las lesiones gruesas en tanto que las infecciones primarias han sido intocadas o áun alentadas.

3) Al principio del siglo XX en los Estados Unidos, un pequeño grupo de médicos empezaron a recomendar la protección de los niños contra la infección primaria.

4) Esto fué tenazmente combatido sobre la base de que tales infecciones protegen contra la enfermedad clínica subsecuente.

5) La oposición fué parcialmente vencida y se construyeron sanatorios para el aislamiento de personas con la enfermedad contagiosa. Una campaña en toda la nación a fin de educarla, se emprendió. Los veterinarios emprendieron la erradicación nacional de la tuberculosis lo que fué un factor de gran poder para prevenir la infección primaria entre las gentes y entre los animales.

6) El resultado fué fenomenal. La mortalidad para todas las edades en los Estados Unidos decreció 82 por ciento entre 1915 y 1949, y 94 por ciento entre los niños pequeños durante el mismo periodo. En Nueva York, entre niños menores de 15 años la mortalidad decreció aproximadamente 94 por ciento entre 1915 y 1948. El ataque de la infección primaria cayó a menos de 1 por ciento por año en muchos lugares, una pequeña fracción del 1 por ciento en otros y la infección primaria desapareció entre los niños de muchas escuelas.

El destino de los cadáveres de animales de ganado a los tanques de destrucción descendió entre 1917 y 1951. En 1951 la incidencia de la infección tuberculosa en el ganado decreció a 0.14 por ciento. En grandes regiones la infección primaria del ganado fué suprimida.

7) A medida que la tarea progresó las teorías erróneas fueron substituidas por los hechos, así: (1) El tipo de tuberculosis bovina que por mucho tiempo se creyó era de poca virulencia para el hombre, produce una enfermedad incapacitante y mortal en las personas así como el bacilo humano. (2) El bacilo de tipo bovino, como se encontraba en los productos de la leche tan altamente recomendado para proteger a los niños contra la enfermedad clínica mas tarde, fué encontrado no solamente inseguro sino que no posee cualidades inmunizantes de confianza. (3) No se ha encontrado base en los hechos, al concepto de que al protegerse a las personas y a los animales contra la infección primaria se crearía "terreno virgen" para los ulteriores ataques de la tuberculosis. Tanto las personas como los animales responden en la edad adulta como lo hacen en la infancia.

8) La menor incidencia de la infección primaria ha proporcionado a los luchadores contra la tuberculosis las mejores posiciones de combate de todos los tiempos. Así el bacilo tuberculoso ha sido puesto de relieve donde puede ser atacado directamente por los métodos mas refinados.

9) Esta situación permite el uso extenso de la reacción de la tuberculina por la que la presencia de la infección primaria puede ser descubierta dentro de los dos meses de la invasión por el bacilo tuberculoso. La inspección periódica por la película de rayos X de

los reactores a la tuberculina localiza las lesiones de reinfección crónica en un término medio de un año y medio antes de que causen síntomas, y generalmente antes de que liberen bacilos al exterior. Las lesiones encontradas en esta etapa de evolución pueden tratarse generalmente en un tiempo mucho menor que las que han llegado a la etapa mas avanzada y son contagiosas.

10) Este método ha estado en uso por un tiempo suficientemente largo y en regiones grandes para demostrar su eficacia. Es el único método conocido hoy por el cual puede erradicarse la tuberculosis.

11) La lepra fué suprimida en Inglaterra y en la mayoría de los países de Europa Occidental al final del siglo XVI por el aislamiento de los leprosos en los leprosarios para proteger al público del contagio. La supresión de la tuberculosis puede lograrse como para la lepra evitando que las infecciones primarias se desarrollen en las personas y en los animales no infectados. Tales infecciones se han prevenido en una parte grande de nuestra población humana y animal. La prosecusión de estos métodos es adecuada. La erradicación de la tuberculosis en cualquier grupo humano o nación puede anunciarse, no cuando la gente y los animales dejen de caer enfermos y de morir, sino cuando las infecciónes primarias desaparezcan.

RESUME

1) La primo-infection est la source de toute la tuberculose.

2) De nombreuses tentatives pour lutter contre la tuberculose ont été dirigée contre les lésions importa tes alors qu'on ne faisait rien pour étouffer la primo-infection, et qu'au contraire quelquefois on en favorisait l'apparition.

3) Très tôt, au début du XXème siècle aux Etats-Unis, un petit groupe de médecins commença à soutenir la nécessité de prendre des mesures de précaution contre la primo-infection.

4) On opposa fortement à cette tentative la notion que de telles infections sont une protection contre la maladie ultérieure.

5) L'opposition fut partiellement vaincue, et l'on construisit des sanatoriums pour les malades atteints de formes contagieuses. Une campagne d'éducation nationale fut instituée. Les vétérinaires organisèrent un programme national d'éradication de la tuberculose, qui fut un élément puissant dans la prévention de la primo-infection de l'homme et de l'animal.

6) Les réalisations furent considérables. Aux Etats-Unis, les moyennes de mortalité pour tous âges diminuèrent de 82% entre les années 1915 et 1949; pendant la même période, cette diminution fut de 94% chez les nourrissons. Dans la ville de New-York, pour les enfants âgés de moins de 15 ans, la moyenne de mortalité diminua approximativement de 94% entre 1915 et 1948. Les mani-

festations de la primo-infection tombèrent à une petite fraction de 1% dans d'autres. Les primo-infections disparurent complètement chez les enfants dans de nombreuses écoles.

Le nombre de cadavres de bétail éliminés du marché diminua de 98.6% entre 1917 et 1951. En 1951, la fréquence de l'infection tuberculeuse chez le bétail tomba à 0.14%. Dans de vastes territoires, la primo-infection du bétail à été complètement supprimée.

7) A mesure que le travail s'avançait, les théories fausses furent remplacées par les faits suivants: (a) le bacille tuberculeux bovin longtemps considéré comme étant de moindre virulence pour l'homme est susceptible d'être à l'origine d'une maladie qui créé autant d'invalides et de morts que le bacille de type humain. (b) Le bacille bovin qui avait été considéré comme capable de protéger les enfants contre la tuberculose ultérieure se montra non seulement dangereux mais encore incapable de créer une immunité. (c) On ne trouva aucun fondement solide à la notion que la protection des hommes et des animaux contre la primo-infection était susceptible de créer un terrain vierge sensible à des attaques ultérieures de la maladie. En effet, aussi bien les hommes que les animaux se comportent devant la primo-infection de la même façon lors-qu'ils sont adultes que dans les premiers âges de leur vie.

8) La diminution de la primo-infection a permis à tous les moyens de lutte contre la tuberculose d'obtenir une situation supérieure à celle qu'ils ont jamais eue. Le bacille tuberculeux peut maintenant être attaqué par de nouvelles méthodes.

9) Cette situation permet l'usage étendu de tests tuberculiniques, grâce auxquels l'existence de la primo-infection peut être décelée dans les deux mois qui suivent l'infection par le bacille. Des radiographies systématiques du thorax chez les porteurs de réactions positives montrent l'existence de lésions pulmonaire chroniques de réinfection, dans une moyenne de deux ans et demi avant qu'apparaisse le moindre symptôme et habituellement avant que soient mis en liberté des bacilles tuberculeux dans l'expectoration. Les lésions qui sont découvertes à ce moment de l'évolution sont habituellement susceptibles d'etre traitées avec succès en beaucoup moins de temps que celles qui sont plus avancées et qui appartiennent à des formes contagieuses.

10) Cette méthode à été utilisée depuis un temps suffisamment long et dans un dommaine suffisamment étendu pour prouver son efficacité. C'est la seule méthode que nous connaisson actuellement qui puisse amener l'éradication de la tuberculose.

11) En isolant les malades dans les léproseries, de façon à protéger l'ensemble de la population contre la contagion, on a pu supprimer la lèpre en Angleterre et dans la plus grande partie de l'Europe Occidentale dès la fin du 16ème siècle. On peut supprimer

radicalement la tuberculose, comme on l'a fait pour la lèpre en empêchant les primo-infections chez les individus et les animaux non infectés. Ces infections ont déjà été prévenues dans un large secteur de notre population humaine et animale. Il est judicieux de continuer les méthodes actuelles. On a le droit d'annoncer l'éradication de la tuberculose dans certaines collectivités ou certaines nations non pas quand les individus et les animaux cessent d'être atteints de la maladie et d'en mourir, mais à partir du moment où les primo-infections ont disparu.

Discussion

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In the time allotted to me I shall comment on but a few of the points raised in Dr. Myers' comprehensive presentation. What I shall express are some of my thoughts which are stimulated by his paper.

In order to tailor a tuberculosis control program to the tuberculosis problem in any area it is necessary that we have a knowledge of how individuals in the community are affected by tuberculosis. We know that the pattern of interplay between the bacillus and the host varies considerably between different communities and different sections of communities. To learn what these patterns are requires longitudinal study of representative groups of the local population by age, race, sex, and location, utilizing tuberculin sensitivity status, morbidity status and mortality events as measurable occurrences in the evolution of tuberculosis. Such data can best be presented by life-table techniques to show changing conditions. For example, the newer techniques of therapy may not change the final case fatality ratio but might greatly prolong the years of life for each case.

There are few communities that have done this. That it must be done, however, is indicated by the many reports that are at variance with each other. For instance, while Dr. Myers takes the position that clinical disease commonly develops many years after infection with tuberculosis, others feel that it is in the first two years after infection that an individual is at great risk of developing clinical disease.

Factors contributing directly and indirectly to man's resistance to tuberculosis are so many and so indefinite and the distribution of tuberculosis so wide, it seems unlikely that the effect of a "virgin soil" will be clearly demonstrated in our lives. Certainly

we have not yet seen evidence that epidemics of tuberculosis result even in the presence of the decreased tuberculin sensitivity which has been attained in the United States. The tuberculinization theorists may advance the counter proposition that we have not yet arrived at a point where a high proportion of tuberculin negative persons have been present sufficiently long to reverse the downward sensitivity, morbidity, and mortality trend. But there is no evidence that any area which now has high sensitivity, morbidity, and mortality ever previously had such a low sensitivity status that one could postulate that the present severe tuberculosis problem resulted therefrom.

The bovine tuberculosis control program does give us warnings as well as examples. Despite widespread tuberculin testing of cattle, we can not say that tuberculosis has been eradicated in cattle if absence of primary infection is our measure of eradication. Yet much has been accomplished, as Dr. Myers has cited, through testing, condemnation and pasteurization. It is my understanding that the interval between tests has been greatly lengthened from one to six years. Since the normal life span of cattle usually runs from 7 to 9 years, this represents an enormous relaxation of vigilance against bovine tuberculosis. Today there are few known cases of bovine tuberculosis in humans. This low recorded incidence, however, may be only a reflection of incomplete laboratory diagnosis, where cultures—artificial and animal—are not used. I believe it timely for laboratories to institute procedures which will permit precise observations, and provide a better picture of the epidemiology of bovine tuberculosis among humans.

Another thought which occurs to me concerns the title of Dr. Myers' paper. I should like to turn it about and ascribe the diminished incidence of primary infection to the tuberculosis control program—a program which is aimed at eliminating exogenous infection through, first, source detection—whether it be by tuberculin testing and periodic x-ray films of positive reactors, or by chest x-ray films alone—and, second, case isolation and management. Like him, I am convinced that vigorous prosecution of these principles will lead to rapid control, if not to eradication as Dr. Myers defines it.

Some Observations on the Testing of Pulmonary Function*

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"The final test for respiratory function of the lung" said the late Max Pinner[1] "is the maintenance of normal oxygen saturation of the blood within physiological limits of stress and a CO_2 output sufficient to maintain the normal CO_2 level in the blood." In the normal lungs the arterial CO_2 tension remains constant even under severe exercise, whereas there comes a point at which the venous blood entering the inadequate lungs is not completely oxygenated. This is why one of the most satisfactory estimates of pulmonary function has been the clinical one, in which the clinician measures the amount of exercise the patient is capable of undertaking before signs of distress appear. For reasons which will be discussed presently, the accompanying changes in the arterial blood have not been used as a more exact means of measurement.

The following experiments were undertaken in order to test a new method for sampling the alveolar air as an aid to the investigation of pulmonary function without recourse to the uncertainties and difficulties of blood sampling and analysis. Grollman[2] for instance has pointed out that the introduction of a needle into an artery produces a rise in the cardiac output of at least a litre a minute, which is of course accompanied by changes in the composition of the circulating blood, and in order to eliminate such variations in the following experiments a plastic polyvinyl catheter was introduced into the brachial artery 30 minutes before sampling, using a technique described recently by Schnabel et al.[3] It was thus possible to obtain simultaneous blood and alveolar air samples from a series of seven young male subjects under conditions of absolute rest. The sampling was arranged in the following order: first, one blood sample was removed, an amount sufficient for two analyses, followed immediately by three alveolar air samples at two minute intervals, and finally by another blood sample. On two subjects (one and three) it was not possible to obtain the second blood sample.

Since the method used for collection of the alveolar air is de-

*This experimental work was carried out in the Department of Physiology, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, with the aid of a grant from the American Heart Assn.

scribed in detail elsewhere[3,4] it will only be outlined as follows: The subject breathes at rest through a rubber mouthpiece at B (Figure 1) with his nose clipped. When the operator desires to collect a sample of the alveolar air, the tap A is turned through one complete rotation at the moment that the rubber indicator at H has reached its maximum swing, and is beginning to drop back into place, that is, at the end of a normal expiration, so that the whole procedure may be complete before the next inspiration starts. This manouver shuts off connection with the outside air at H during the whole rotation, and also brings into action the previously evacuated rubber bulb E which removes 180 cc. of gas from the oral cavity. The bulb washes out the lead with alveolar air, and immediately afterwards brings the evacuated barrel F into communication with the lead, thus collecting an uncontaminated sample of alveolar air, and returning the tap A to room air in time for the next inspiration. The tube is then removed and the contents analyzed in the Scholander one-half cc. analyzer.

(It may be noted that the same procedure is followed when gas mixtures are being breathed instead of room air, for the purpose of collecting a sample of "venous" alveolar air.[5,6] The mixture is introduced from the rubber bag K which is connected to a continuous stream of gas from a cylinder and fitted with a "flutter" valve to keep the pressure constant. The subject is switched from room air to mixture by pulling over the lever G at the end of a normal expiration, so that the mixture is in position for the next inspiration without disturbance to the respiration. In the diagram the slide valve is shown fitted with a manifold of several rubber bulbs instead of the usual one, to permit of the simultaneous removal of any desired volume of gas, should it be necessary to examine the composition of the alveolar air at any desired depth in the lungs. After the required number of breaths (one or two according to which method is employed), tap A is turned and a sample of alveolar air collected. Although estimations of the venous CO_2 tension, CO_2 output, and cardiac output were carried out at the same time in the present series, it is not proposed to include them, but attention is drawn to the separate publication,[6] in which it is shown that, providing enough CO_2 is inspired, the pulmonary vascular bed appears to assume the CO_2 tension of the incoming venous blood within the space of a few seconds, the surplus CO_2 being as quickly removed by the pulmonary vein. This presents a means of estimating the CO_2 tension of the venous blood entering the lungs, giving further information regarding the pulmonary circulation).

Table I shows how closely the CO_2 tension of arterial blood and alveolar air agreed in the foregoing experiments. There is in fact

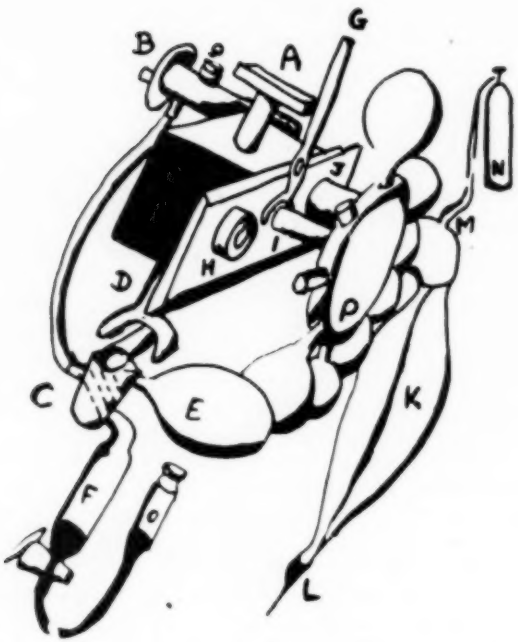

FIGURE 1: Modification of the Forssander-White apparatus for examining the arterial and venous alveolar air.

A. Sampling tap. This connects mouth to room air only in one position in the full rotation.
B. Mouthpiece, with tube leading to suction tube.
C. Suction tube communicating consecutively with rubber bulb and evacuated sample barrel during one complete rotation.
D. Clasp, rotated by Tap A, which holds the cock of suction tube.
E. Rubber bulb of 180 cc. capacity which evacuates oral cavity and washes leads out with alveolar air.
F. Evacuated sampling barrel.
G. Handle to enable slide valve to be moved from room air to bag aperture rapidly.
H. Room air aperture, with latex indicator.
I. Opening for suction manifold, which is applied automatically during the passage of the slide valve.
J. Bag aperture, to which is affixed a 2 litre rubber bag containing gas mixtures.
K. Rubber bag.
L. Expiration "flutter" valve, which maintains a constant pressure in the bag.
M. Inlet for CO_2 mixture supply.
N. Gas cylinder.
O. Mercury reservoir for evacuating sampling barrel.
P. Manifold, to which any desired number of evacuated rubber bulbs may be fixed.
Q. Point at which an expiratory valve may be fixed if required.

no statistical difference. If we examine the difference of the means (since all the results are so close), this is seen to be only .11 mm. Hg. provided we reject the results on subject number six where, even neglecting the first high blood sample (45.5) the difference between blood and alveolar air is still definitely larger than the rest. However, if we include subject number six, omitting the high result, the difference of the means is only 0.05, which is still well within the range of the experimental error.

This confirms in the most direct manner that the relationship between the blood and alveolar air carbon dioxide is intimate, and that changes in the partial pressure of carbon dioxide in the arterial blood can be examined satisfactorily without recourse to blood sampling. The importance of this is discussed below, since it has not hitherto been possible to examine the uncontaminated alveolar gases without co-operation from or disturbance to the patient.

Discussion

The clinician requires a procedure which does not demand a trained staff for application and interpretation, and which can

TABLE I

Subject	Arterial Blood CO_2 mm. Hg. (1) (a)	Mean	Alveolar Air CO_2 mm. Hg. (2) (b)	Difference (a)-(b)	Percentage Difference
1.	35.0	35.0	34.07	−0.13	−0.37
2.	38.8 39.4	39.1	39.20	+0.10	+0.27
3.	34.5	34.5	35.01	+0.51	+1.45
4.	44.5 44.3	44.4	45.30	+0.90	+2.02
5.	43.8 41.0	42.4	41.79	−0.61	−1.43
6.	(45.5) 39.7	39.7	38.49	−1.21	−3.05
7.	41.5 40.3	40.9	41.59	+0.59	+1.44
	Mean	39.8	39.49	0.11	
(Omitting subject 6). Average per cent difference					= .047

(1) On subjects one and three blood samples were taken (by means of an indwelling polyvinyl catheter in the brachial artery) prior to sampling the alveolar air. On the other dates blood samples were also taken after the alveolar air samples.

(2) Each figure represents the mean of three consecutive alveolar air samples.

be used on sick people. He is interested in estimating the relative efficiency of emphysematous lungs, and in obtaining a reliable forecast of the functional result in his surgical cases. Unfortunately no current test alone is capable of giving reliable information under all circumstances, and the one most easily applied and in widest use, the vital capacity estimation, often presents serious divergences from the clinical assessment.[7] It is essentially volumetric and takes little account of changes in lung vascularity. Destruction of pulmonary vessels or pathological changes must inevitably reduce the total, and probably the relative vascular capacity. The extent of this ability to present an increasing volume of venous blood to the alveolar air for oxygenation is a measure of the efficiency of the lungs, and when this is exceeded in the course of effort the CO_2 tension of the blood leaving the lungs rises, and subjective symptoms appear.

The recent work by Glaser et al.,[8] and by Kjellberg et al.[9] using radiological techniques gives strong support to the view that the lungs act as a physiological blood depot, a concept that had been substantiated by Mills[10] in his investigations of the vital capacity. This is important if we consider that the efficiency of the lungs may be judged by their ability to aerate an increasing volume of venous blood, primarily a vascular problem only indirectly related to the vital capacity. The experiments of Borden et al.[11] supply corroboration; pressures were taken from the pulmonary arteries of emphysematous patients and found to be raised in spite of the cardiac output remaining normal, indicating an increased vascular resistance. These same workers also found[12] that patients with severe emphysema have no ventilatory control over the CO_2 tension and pH of the arterial blood, so that whatever ventilation was achieved was ineffective, and with voluntary hyperventilation they found that there was only a small increase in excreted CO_2 (indicating a decrease in the efficiency of aeration) which contrasted with the results in cardiac cases (where the pulmonary vascular bed was intact). Marchand et al.[23] have carried out anatomical studies of the vascular pattern in 39 normal lungs and 24 diseased, and have found anastomoses between bronchial and pulmonary arteries more numerous in the diseased lungs, which they consider to be of very great importance in their effect on the haemodynamics of the pulmonary circulation in disease.

An attempt has been made in Figure 2 to summarize these new findings diagrammatically as they suggest a "vascular reserve" in the lungs, physiologically as important as the vital capacity and potentially capable of measurement.

Measurable variations in mixing of inspired gases with the alveolar air exist under some circumstances[14] and the new "cap-

acity" terms referring to subdivisions of the lung volume, adopted at Atlantic City in April 1950,[15] have some advantage in the clinical application of volumetric pulmonary function tests, but they do not entirely represent a break from the 19th century "mechanistic" concepts from which the science of Physiology is only gradually freeing itself, and it is evident that many apparent variations in the composition of the alveolar air reported in the past have actually been variations in the methods of collection and analysis.

It is therefore important to define carefully what we expect of a pulmonary function test. Bateman[16] feels that "the search for tests of adequacy of ventilation reduces essentially to the attempt to relate measurable respiratory characteristics to a more or less abstract system of unknown "alveolar" partial pressures and respiratory deadspace, and to relate this, in turn, to the composition and distribution of blood entering and leaving the vessels of the

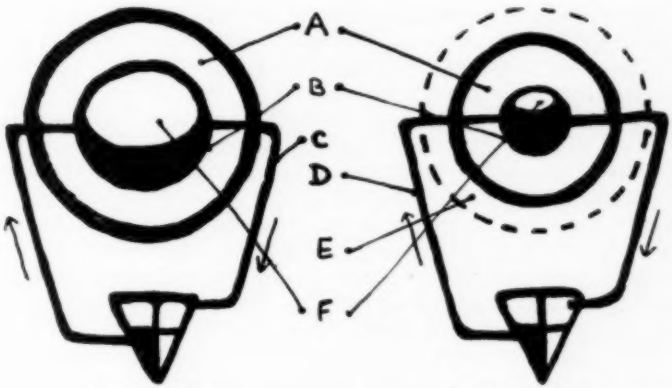

FIGURE 2

A. Alveolar air.
B. Pulmonary vascular bed.
C. Pulmonary vein.
D. Pulmonary artery.
E. Impaired portion of lung.
F. "Pulmonary vascular reserve."

Although A is reduced in the impaired lungs, and as a result the amount of oxygen available is less, the important feature is the accompanying reduction in the vascular bed. While the cardiac output entering from the pulmonary artery remains a resting one, the area of blood presented for aeration may be adequate. An increase in the output of blood from the right ventricle, however, soon comes up against the limitation in the vascular bed, and more venous blood enters than can be efficiently oxygenated during its passage through the lungs; the CO_2 tension of the blood in the pulmonary vein rises, and subjective symptoms appear.

lungs." Some aspects of the problem have presented difficulties, and Ornstein et al.[17,18] who have themselves made very interesting assessments of the vascular component of pulmonary function, have remarked that "a good deal of attention has been directed to the ventilatory phase of lung function, and too little to the diffusion of gases in the lung tissue." The reason for this has been the lack of an adequate technique for examining the blood-alveolar air relationship. It has been impossible to obtain a reliable estimate of the partial pressure of the gases in equilibrium with the blood in the pulmonary vascular bed, without disturbing that equilibrium, and thereby confusing the values obtained.

The respiratory physiologist has approached from many angles with varying degrees of success; essentially his problems have divided into three parts: (a) *Collection* of alveolar air samples, (b) *Analysis* of the gas samples, and (c) *Interpretation* of changes in the composition of the alveolar air.

(a) *Collection* of alveolar air has been most accurate when the subject has been trained to blow rapidly from his lungs into a long tube which has a sampling bottle attached at the end near the mouth. This method was found by Haldane and Priestley who described it originally,[19] and many workers since, to give results which approximated very closely to the gas partial pressures in the blood. Even with this method, however, accuracy is only obtainable under certain conditions, and as a result a good deal of confusion has arisen.

For instance, the subject must be trained to deliver samples smartly at the end of a normal expiration without any pause whatsoever. A common mistake is that expiration takes longer than normal because the subject has the impression that purer gas will come from the deeper parts of the lungs. In fact some writers make a point of insisting on a maximal expiration, although Haldane himself did not share this belief, the fallacy of which is shown by comparisons of the Haldane-Priestley method with the Oral Suction Method (infra), in which the *efficient* removal of only 180 cc. (a little more than the volume of the anatomical deadspace) of gas from the oral cavity immediately at the end of a normal expiration produced results approximating very closely to Haldane-Priestley samples; and also by the experiments of Lambertsen et al.[20] in which sampling was made from the last part of each normal expiration from the tracheal bifurcation using a catheter inserted through the cricothyroid membrane, when no statistical difference was found between these samples, arterial blood, and Haldane-Priestley samples. In fact, as has been pointed out elsewhere[6,11] a deep expiration is likely to be fallacious as it is the equivalent of breath holding if the

time exceeds that normally occupied by the end expiratory pause, since venous blood is entering the lungs during that time.

Herber[21] has shown in dogs subjected to rebreathing that the alveolar CO_2 rises indefinitely until death, and Haldane[22] tried to use this fact in order to estimate the CO_2 tension of the mixed blood, but failed because recirculation occurred before equilibrium could be established. Hamilton et al[23] have also pointed out that rebreathing and breath holding are physiologically similar and that the CO_2 increase is due to the rising *mean* tension of the pulmonary vascular bed as the venous blood enters from the pulmonary artery. This is an important concept which has been neglected in considering changes in the alveolar air, and may be stated briefly as follows: During normal breathing the mass of blood in the lungs is of arterial composition, and any externally-imposed pause in the respiration results in an increase in the CO_2 content of the pulmonary vascular bed; the blood leaving the lungs is inefficiently oxygenated; the alveolar air (and blood) CO_2 rises steadily as venous blood enters from the pulmonary artery, and if the pause lasts more than about 12 to 15 seconds (less during exercise because of the increasing cardiac output) the CO_2 in the arterial blood leaving the lungs begins to re-enter the lungs on the venous side from the shortest routes (e.g. the coronaries) and the venous CO_2 (and therefore the alveolar air CO_2) rises steadily. Although the complete pulmonary circulation takes about 10 seconds at rest,[24] Roughton[25] has recently shown that the time during which the blood is presented for gas exchange is less than a second, and it is possible to see how the entire vascular bed responds so readily to changes in the partial pressure differences between incoming blood and alveolar air, when the time of replenishment of the alveolar air is delayed by a respiratory pause. Thus evidence accumulates and shows that some of the older ideas as to the nature of the pulmonary circulation will have to be modified.

The deadspace air exerts a significant influence on the composition of the expired air,[3] and also of the inspired air,[26] and the real value of the forcible expulsion of gas is in the clearing action it has on the upper respiratory tract, where no respiratory exchange is taking place. Therefore the force and time of the expulsion is of more importance than the volume. Forssander[6] has shown by removing varying volumes of gas from the lungs that the CO_2 content is the same at different levels, providing the time is not variable, and providing also that the deadspace air is removed before sampling.

Other methods relying on the principle of Voluntary Expulsion have not been so successful, for instance, the Henderson-Morris

method[27] requires the subject to suck acidulated water into a tube before delivery; the sample therefore contains an abnormally large amount of CO_2 owing to the delay. The Fridericia method has a similar error owing to the resistance to expulsion produced by the shape of the apparatus.

Riley et al.[28] devised an indirect method for calculating the composition of the alveolar air which is not subject to errors introduced by time and space factors, and this has been found to give good values, but has obvious limitations.

Numbers of attempts have been made to design an automatic method, most of which have depended on some variation of the principle, introduced by Krogh and Lindhard[29] of using the last part of the expiratory tidal volume. These methods have had the advantage that they require no co-operation from the subject, and therefore are potentially suitable for clinical application. However, they have all suffered from the disadvantage that the CO_2 tension of samples collected in this way was lower than that of the arterial blood. Rahn,[30] whose method is one of the most recent, has found that his figures were on an average 2.5 mm. Hg. lower than those obtained by the Haldane-Priestley technique, and Lambertsen et al.[20] have obtained similar results using Rahn's method. The reason for this difference is that end-tidal samples are diluted by the inspired air still contaminating the supra-glottic deadspace.[3]

This latter source of error has been attacked by means of the suction principle. Lambie and Morrissey[31] devised a method involving a piston actuated by a series of electrical relays, in which they accepted consecutive identical samples as evidence that alveolar air was obtained, but unfortunately the method was not standardized against blood samples or Haldane-Priestley samples. Forssander and White[4] developed the simple Oral Suction method which shows no significant difference from, and less variability than the Haldane-Priestley method and it has the special advantage of being suitable for clinical application. Since the air of the deadspace is removed by suction prior to inspiration there is immediate and direct mixing between the inspired and alveolar air. Samples examined represent the composition of the respiratory gases at the moment of taking the sample, which has given additional information not made available by methods in which the time element is variable.

(b) *Analysis* of the alveolar air has been most successfully carried out by means of absorption techniques whereby the carbon dioxide and the oxygen in a gas sample are each absorbed and the reduction in the volume of the sample measured. The Haldane Gas Analysis Apparatus has been the best known, and recently Scholander[32] has introduced an analyzer which has important ad-

vantages in that it requires only a half-cc. of gas, a few minutes for each analysis, and has an accuracy of 0.015 volumes per cent. This latter apparatus has opened up fields of respiratory investigation not previously possible.

Numbers of continuous methods of analysis have been developed: the most important being described by Rahn[30]; by Lilly[33] who has designed a nitrogen meter capable of measuring to the nearest 0.5 per cent; the promising rapid infra-red CO_2 analyzer at present being used by Dubois et al[34]; and the mass spectrometer applied by Stacey and Kidd.[35] These methods as applied at present analyze the end-tidal air, not the alveolar air, but it should be possible to eliminate the deadspace contamination during the use of these continuous methods. In the meantime it is true to say that continuous methods of analysis present variations which it is wise to bear in mind during interpretation, unless one is interested only in the broader changes in the alveolar air.

(c) *Interpretation* of changes in the composition of the alveolar air always requires consideration in the light of the techniques employed:

(1) *Deadspace* contamination has been referred to above, and is regarded by the present author as an important and frequent source of error.[8] The rate and manner of expulsion is likely to be different in sick and healthy people, and one must consider that variations in deadspace clearance can be interpreted as changes in intrapulmonary mixing.

(2) *Time* has also been referred to. Many pulmonary function procedures require voluntary efforts on the part of the patient which necessarily demand a variable degree of breath holding. This inevitably results in a rise in CO_2 tension of the pulmonary vascular bed.[11]

(3) *Partial Pressure gradient between the blood in the pulmonary arteries and the alveolar air* has been referred to by Stacey and Kidd.[35] It remains to be seen whether pathological changes in the alveoli produce any measurable change in the gradient.

(4) *Deep inspirations* must be considered in relation to variations in the pulmonary vascular bed due to stretching of the vessels, time (supra) and mechanical mixing.

(5) *Mixing*. From time to time since the early part of the century the hypothesis of unequal mixing of the inspired air with the alveolar air has been discussed. An intensive historical review has been made by Rauwerda.[36] Various "fractional" sampling techniques have been attempted in order to estimate the composition of the air at various depths in the lungs, but the time elapsing between one sample and the next has always been long enough to make interpretation difficult; the introduction of the Oral

Suction technique made possible the virtual elimination of the time element, and it was shown[6] that so far as CO_2 is concerned, under conditions of rest in the normal subject, the alveolar air is homogenous. Drift and delay in continuous analytical methods have to be considered, and also the fact that the composition of the end-tidal air varies with the part of the stream from which it is taken. The use of rubber bags in the study of mixing problems has always been a source of confusion since it has been difficult to differentiate between mixing in the bag and in the lungs; the lungs in no way may be compared physiologically with bags (although they are commonly, but mistakenly), and rebreathing has had the disadvantage of adding an enormous extra deadspace with the attendant sources of error discussed above. Bazett et al.[37] have pointed out that although the impression can be drawn from past literature that adequate mixture of gases in the lung is not likely within 15 seconds with a quiet respiration, the altering ratios of the blood stream returning from different areas of the body (during the course of breath holding or voluntary breathing procedures) have caused unwarranted conclusions on gas mixing.

It is evident that any method for estimating the efficiency of pulmonary function must be independent of a large number of possible sources of error.

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SUMMARY

In pathological conditions involving destruction or impairment of lung tissue the vital capacity is reduced; owing to the adaptability of the vascular system in the lungs there is not necessarily any direct relationship between the area of impaired tissue, or change in air-containing volume of the lungs, and the amount of blood that is exposed for aeration. The capacity of the pulmonary vascular bed may be adequate for a resting cardiac output of about five litres a minute, but even moderate exercise more than doubles this output of venous blood into the lungs, and the remaining "vascular reserve" may not be adequate to deal with the increased volume efficiently, in which case the CO_2 tension of the blood increases. This increase can be measured by a simple method, and provides for investigation a means of observing the efficiency of pulmonary function.

RESUMEN

En condiciones patológicas que incluyen destrucción o deterioro de el tejido pulmonar, la capacidad vital se reduce; debido a la adaptabilidad del sistema vascular en los pulmones no existe necesariamente relación entre el área de tejido deteriorado ni el cambio en el volumen de aire del pulmón, y la cantidad de sangre expuesta a la aeración. La capacidad del lecho vascular pulmonar puede ser adecuada para un rendimiento cardiaco en reposo de cerca de cinco litros por minuto, pero aun el ejercicio moderado aumenta a más del doble la entrada de sangre venosa a los pulmones y la restante "reserva vascular" puede no ser adecuada para hacerse cargo del volumen aumentado eficientemente, en cuyo caso la tensión del CO_2 de la sangre aumenta. Este aumento puede ser medido por un método sencillo, y provee a la investigación de medios para observar la eficiencia de función pulmonar.

RESUME

Dans certaines conditions anatomiques qui comprennent des destructions ou des lésions du tissu pulmonaire, la capacité vitale est réduite. En tenant compte des possibilités d'adaptation du système vasculaire dans les poumons, il n'y a pas nécessairement relation entre la surface de tissu lésé ou dans les altérations du volume contenu dans les poumons, et la quantité de sang qui est susceptible d'être oxygénée. La capacité du système vasculaire du poumon peut convenir à un débit cardiaque en phase de repos d'environ cinq litres par minute. Mais un exercice, même modéré, peut plus que doubler le débit du sang venu dans les poumons, et la "réserve vasculaire" restante peut n'être plus suffisante à contenter cette augmentation de volume. Dans ce cas, la tension du CO_2 du sang augmente. Cette augmentation peut être mesurée par une méthode simple et offre ainsi un moyen de mettre en évidence l'état de la fonction pulmonaire.

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Exploratory Surgery of the Heart*

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With the amazing recent development of cardiac surgery and its coming to mature stature as a recognized specialty, it was inevitable that the concept of exploratory surgery of the heart should soon be definitively promulgated. After all, exploratory surgery has long been accepted for obscure or uncertain conditions in practically every other part of the body. Why not for the heart?

There are certain obvious reasons. First, the idea of surgery of the heart carries with it certain emotional reactions and inhibitions which interfere with calm, dispassionate and logical reasoning. One must subconsciously insist—"Why should they not be certain of the diagnosis before operation? Isn't the operative mortality very high even when the diagnosis is clearly recognized?" The second objection is based upon the realistic consideration that some severe cardiac cripples may not be able to stand exploratory operation well. Suppose no definitive or corrective operation is found possible? Will the patient survive the exploration?

The former objection may be answered simply by pointing out that present diagnostic methods are not sufficiently accurate to certainly reveal the diagnosis preoperatively in all cases. Some 15 to 20 per cent of cases will not be found diagnosable by diligent application of all our presently available clinical and laboratory facilities. Unless exploration is then carried out in order to clarify the diagnosis and in the hope of being able to immediately correct the abnormal condition by mechanical means, the patient must be denied his chance for improvement by surgery. The mortality of practically all extra-cardiac major vascular operations today is less than 10 per cent. The mortality for intracardiac operations is closely approaching that figure. Again, one must admit that even the most carefully established diagnosis may be found to be incorrect at the time of operation. Rather than to retreat in confusion, it is then the surgeon's duty to promptly identify the problem and to apply the proper therapy.

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if any. It must also be recognized that while the preoperative diagnosis may be confirmed at operation, additional unsuspected abnormalities may be found. They may then, under certain conditions, be more completely investigated by one of the methods detailed here, or perhaps may be immediately corrected. A word of caution—in surgery for one of the less serious defects with appropriately low mortality, one should not suddenly change to a more major procedure with higher mortality without discussing the graver problem at least with the patient's family.

The second objection is more valid. Certain seriously ill cardiac patients obviously cannot tolerate any major surgery. They, of course, must not be operated. Others would be able to tolerate surgery providing an advantageous modification or actual correction of the diseased anatomical or physiological state could be accomplished, but would withstand it with difficulty if not relieved.

Cases of cyanotic congenital heart disease frequently present this problem. Unless the cyanosis is improved by proper surgical means, a fair percentage of such cases will not survive exploration. The responsibility for advising and carrying out exploration must weigh especially heavily upon the physician under such circumstances. He must consider the plight of the unfortunate patient if left alone, with respect to longevity, activity, and happiness. He must consider the most probable diagnostic possibilities and the likelihood that some surgical improvement may be accomplished in any of these situations. He must consider the relative chances that may make for survival or death of this specific individual patient. The calculated risk then may be shared with the patient or his family.

Exploratory surgery of the heart, as the name would imply, consists of exploratory operations performed in the hope that some definitive, corrective surgical maneuver might be feasible once the diagnosis is clarified.

In one sense, all surgical operations upon the internal organs of the thorax or abdomen must be considered exploratory. Our existing diagnostic methods and criteria are far from being conclusive in every case. Therefore, some percentage of supposedly certain diagnoses will be disproved at operation, usually with simultaneous substitution of more reliable ones. However, the specific term "exploratory" is understood to refer to operations performed in the absence of a definite diagnosis for a dual purpose—establishment of a diagnosis and immediate mechanical correction,—if possible. Ordinarily an exploratory operation is not employed until reasonably exhaustive non-surgical diagnostic studies have failed to reveal the diseased state.

Because of the recognized seriousness of cardiac surgery and

also of cardio-vascular surgery (surgery of the great blood vessels in an attempt to correct a cardiac disability), all possible reasonable non-surgical diagnostic measures must be employed. Then, if the diagnosis still is not clear, if the apparent seriousness of the case requires taking any reasonable chance for correction, exploration may be contemplated. All reasonable contra-indications to surgery in each specific patient must be observed.

Exploration of the heart may logically be divided into three phases or stages of exploration. (1) Exploration limited to the intact outer surface of the pericardium and the adjacent great vessels in the mediastinum; (2) exploration of the interior of the

FIGURE 1: Palpation of thrill in pulmonary artery through intact pericardium.

pericardium, the surface of the heart and the surface of the intrapericardial great vessels; (3) exploration of the interior of the cardiac chambers and of the interior of the adjacent great blood vessels.

(1) Inspection and palpation of the outer surface of the pericardium will tell us much about the size and contour of the heart. Abnormal thrills and pulsations will suggest certain obstructions, dilatations or abnormal communications. Palpation in the mediastinum may reveal a patent ductus arteriosus or a coarctation of the aorta. Palpation of the aorta may reveal an aneurysm or a systolic thrill at its root, suggestive of aortic stenosis. Dissection

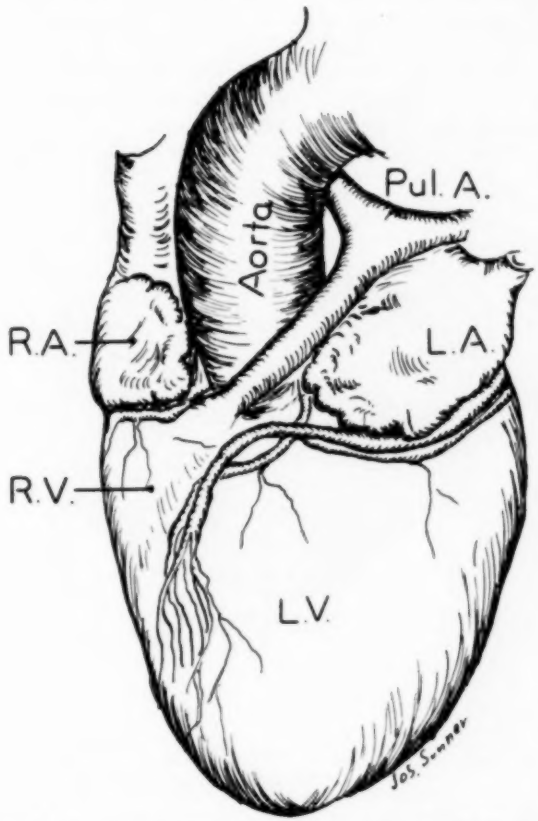

FIGURE 2: Tricuspid atresia manifested by hypoplasia of the right ventricle and pulmonary artery.

of the mediastinal tissues may reveal other abnormalities such as a double aortic arch or other type of vascular ring. Pressures may be determined in the pulmonary artery by direct insertion of a small needle through the wall of the vessel with suitable manometric equipment. Thickening of the pericardium, adherence, or the presence of pericardial effusion can be recognized (Figure 1).

(2) Opening of the pericardium will permit inspection and palpation of the heart itself and will reveal much information. Pressure determinations may now be made accurately in any chamber or great vessel. The over-all size of the heart and the relative size of each chamber may be estimated. Whereas general conditions such as anemia may produce symmetrical dilatation of all chambers, most primary circulatory abnormalities specifically enlarge or diminish one or more cardiac chambers but not all. This differential from normal chamber proportion may be diagnostic. Thus, enlargement of the right auricle alone suggests a tricuspid stenosis. The right auricle, along with the right ventricle is greatly dilated in auricular septal defect and in cases

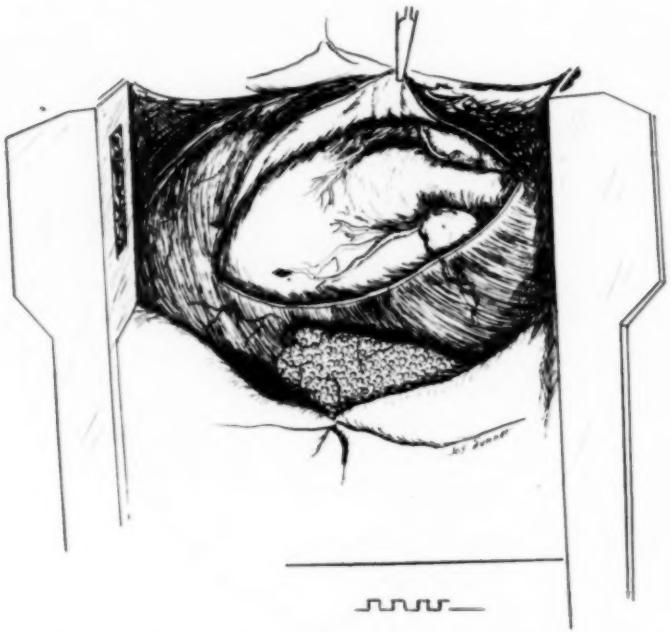

FIGURE 3: Waist-like narrowing in the right ventricle indicating an infundibular septum obstructing the outflow tract.

where all or most of the pulmonary veins empty directly into the right auricle or into the venae cavae.

Proceeding methodically with examination of the heart along the course indicated by the flow of the circulating blood:

In cases of interatrial defect or of tricuspid disease, the right atrium is usually greatly dilated.

A systolic thrill palpable in the right atrium may be due to an interatrial septal defect but usually indicates a tricuspid insuf-

FIGURE 4: Fusiform dilatation of the pulmonary artery distal to a congenitally fused pulmonary valve.

ficiency. In children this insufficiency is usually part of Ebstein's Syndrome. It may also be rheumatic, functional, or congenital.

Dilatation of the right ventricle suggests (a) an obstruction of its outflow tract (in the pulmonary artery, the pulmonary valve or in the infundibulum), (b) excessive pulmonary blood flow due to an auricular or ventricular septal defect, or (c) pulmonary hypertension whether due to primary pulmonary vascular disease or to mitral valve deformity. Absence or extreme hypoplasia of the right ventricle almost always indicates a tricuspid atresia (with an interatrial septal defect) (Figure 2). A waist-like harrowing in the right ventricle or a dilatation of its outflow tract indicates an infundibular septum obstructing the outflow into the pulmonary artery. A systolic thrill will then be felt beyond the obstruction and transmitted up the pulmonary artery (Figure 3). In tricuspid stenosis there is always a localized diastolic thrill

FIGURE 5: Direct manometric determination of pulmonary arterial pressure.

palpable near the apex of the right ventricle above the level of the obstruction.

General dilatation of the pulmonary artery suggests (a) excessive flow as in cases of septal defect (auricular or ventricular) or of emptying of pulmonary veins into the right auricle, or (b) of pulmonary hypertension either due to lung disease, mitral disease or patent ductus arteriosus.

Fusiform dilatation of the first part of the pulmonary artery with a narrowing at its origin suggests a post-stenotic dilatation beyond a congenitally fused pulmonary valve. This can be confirmed by palpation of the localized systolic thrill at one point in the vessel wall, and by digitally invaginating the flaccid wall of the vessel to actually feel the crater-like fused pulmonic valve which erupts with each systole (Figure 4). Direct manometric measurement of pulmonary arterial pressure, determined by a needle inserted into the vessel, is often helpful (Figure 5). In valvular pulmonic stenosis the systolic thrill is palpated in the artery but not in the right ventricle, whereas in infundibular stenosis it is also felt in the outflow tract of the right ventricle.

Hypoplasia of the pulmonary artery suggests general hypoplasia of the right ventricular outflow tract with infundibular stenosis. Usually there will be an associated high interventricular septal defect (Figures 6a and 6b). Stricture or narrowing of a localized segment of the intrapericardial part of the pulmonary artery is readily visualized and suggests the need for surgical dilatation (Figure 7).

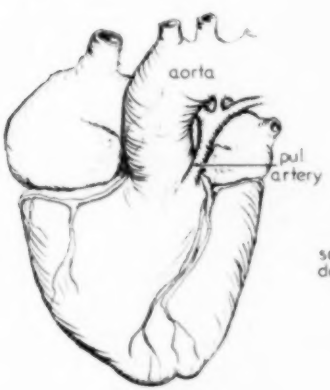

FIGURE 6a

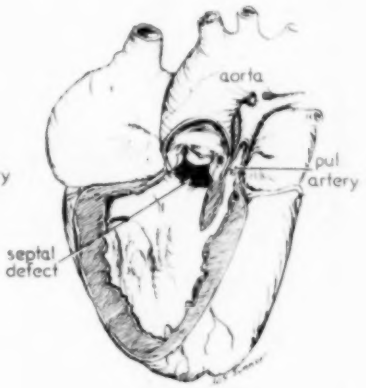

FIGURE 6b

Figure 6a: Dilatation of the right ventricle and hypoplasia of the pulmonary artery.—*Figure 6b:* Section revealing pulmonary outflow tract and high ventricular septal defect.

Transposition of the great vessels is readily diagnosed by observing that the aorta arises from the anterior (right) ventricle. The pulmonary artery then arises posteriorly to it from the posterior (left) ventricle (Figure 8). The transposed pulmonary artery may have free blood flow or may be partially or largely obstructed at its origin. In the latter instance the pressure in the vessel will be found low (by palpation or actual measurement) and there will be a systolic thrill over its course. Lesser degrees of rotation or transposition of the vessels, as seen in various grades of tetralogy of fallot, may be noted. The amount of overriding of the septum by either artery may frequently be estimated. A probe

FIGURE 7: Stricture or narrowing of a localized segment of the pulmonary artery.

inserted into the right or left ventricle and directed into each great artery may be of great help.

A communication between the aorta and pulmonary arteries above the valve level (aortic septal defect) causes a coarse systolic thrill in this portion of the pulmonary artery, and considerable dilatation. Insertion of a small urethral sound through a puncture (guarded by a purse-string) in the pulmonary arterial wall will permit accurate localization and estimation of the size of such a defect (Figure 9).

The pulmonary veins of the left lung can be visualized to enter the left auricle. If they are distended the left auricle, too, is nearly always dilated and usually under increased pressure (since there are no valves between them). Dilatation of the left auricle and

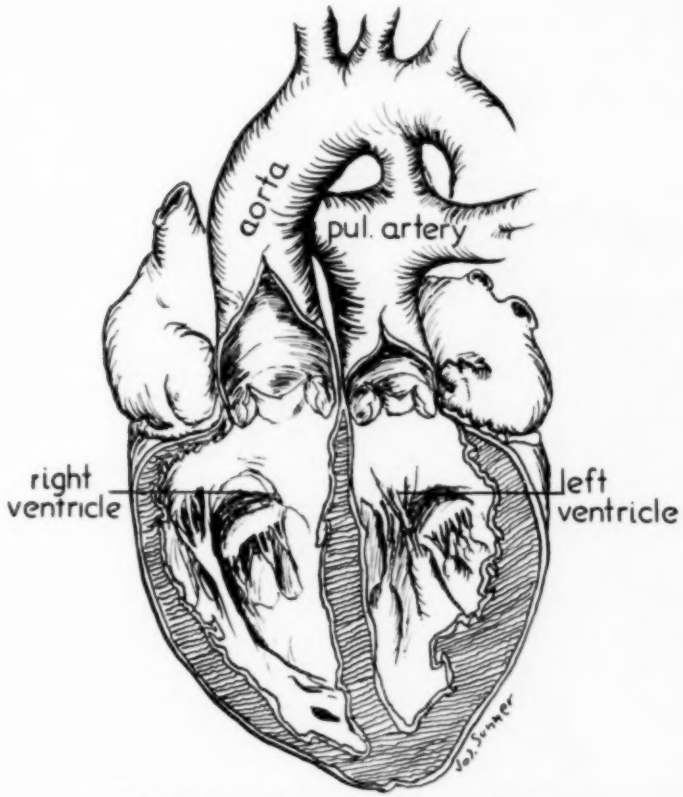

FIGURE 8: Complete transposition of great arteries.

pulmonary veins nearly always indicates a severe degree of mitral stenosis or insufficiency (Figure 10). They are of normal size in cor pulmonale (due to intrinsic lung disease). A systolic thrill palpable in the left auricle or in the pulmonary veins is pathognomonic of severe mitral insufficiency.

In certain cases the left pulmonary veins may not drain into the left auricle. They may then be traced as they pass behind the left auricle to enter the right auricle. More often, in such deformities they empty into a common venous channel which passes within the pericardium, and behind the left auricle to join the superior vena cava. In cases where there is a double

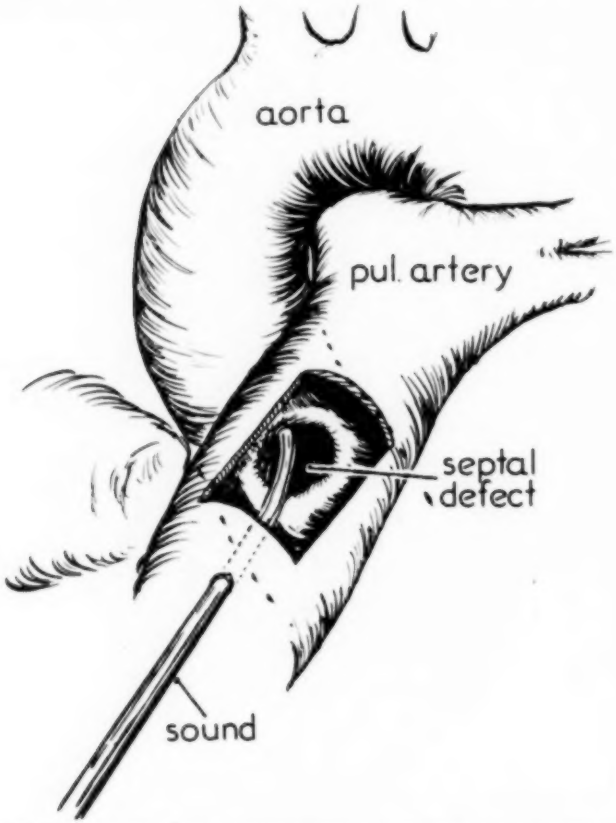

FIGURE 9: Aortic septal (aortico-pulmonary) defect demonstrated by probe inserted through pulmonary arterial wall.

(right and left) superior vena cava with abnormal pulmonary venour drainage, the vessels of the left lung usually empty into the left superior vena cava which in turn crosses to join the right one (Figure 11).

Thrombosis of the left auricular appendage is nearly always due to mitral stenosis usually with associated auricular fibrillation. It may result in a shrunken fibrotic appendage, or may merely be recognizable by palpation of a solid or woody non-compressible appendage. Fresh thrombosis may be difficult to detect except by recognizing slight loss of compressibility.

A small or absent left ventricle may be due to congenital aortic atresia. Here there is nearly always mitral valve atresia and a compensating interatrial septal defect. In such cases the left atrium is normally or abnormally large. These individuals always die in infancy or early childhood, so the occurrence of a small left ventricle and a large left auricle in an adult is practically pathognomonic of the existence of mitral stenosis (Figure 12). This is further corroborated by the co-existence of a large dilated right

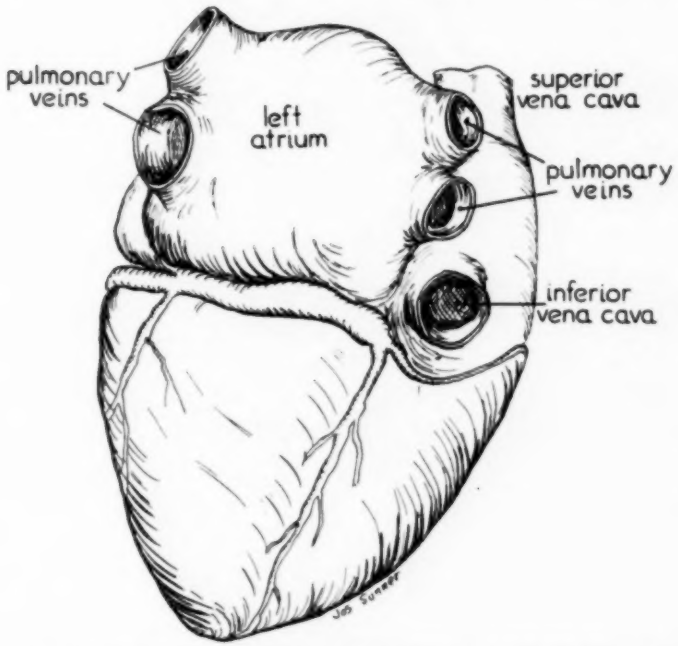

FIGURE 10: Great dilatation of pulmonary veins and left atrium due to mitral stenosis. (From behind).

ventricle. A diastolic thrill localized to a very small area about the left ventricular apex confirms the diagnosis (Figure 13).

In essentially "pure" mitral regurgitation the left ventricle is very large, although the right is also large. The left auricle, too, is dilated. There may be an associated diastolic thrill at the ventricular apex if stenosis co-exists, but not in pure mitral regurgitation. A systolic thrill in the left auricle, when present, is confirmatory of mitral insufficiency.

In aortic stenosis and particularly in aortic regurgitation the left ventricle is also enlarged. Here, the right ventricle may seem disproportionately small. The diastolic thrill of Aortic Regurgitation is felt over the base of the left ventricle, laterally, just over the mitral valve. This is probably the basis of the so-called Austin-Flint murmur. The systolic thrill of aortic stenosis is best felt at the root of the aorta, especially to the right side. It may be largely localized to a small spot on the aortic wall which is

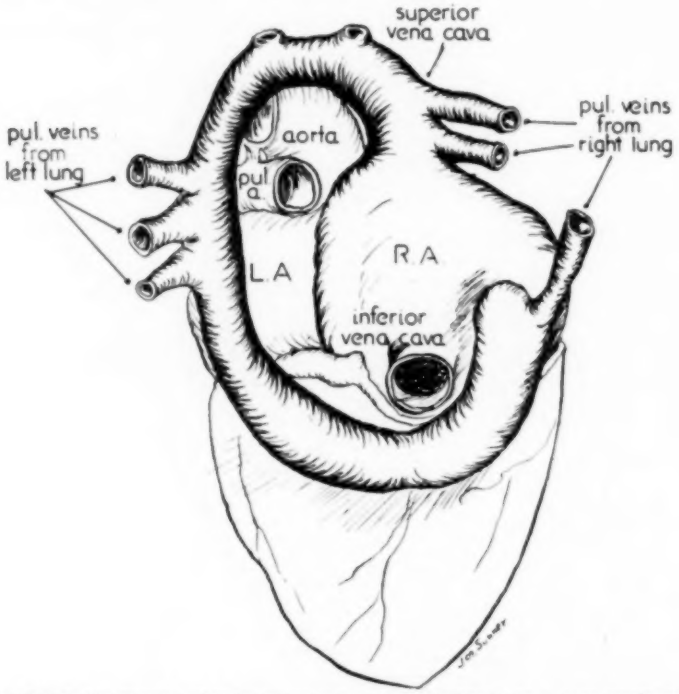

FIGURE 11: Course of pulmonary veins (from behind) in a case explored by us in which all pulmonary veins eventually emptied into the right superior vena cava. A compensating auricular septal defect was present.

directly in line with the high speed jet of blood emerging from the nozzle-like stenotic aortic valve orifice (Figure 14).

Evidences of an old myocardial infarct are occasionally visible over the left ventricle. The pericardium may be adherent over this area, but the involved portion of the heart surface is usually non-adherent, whitish, opaque and fibrotic. Calcification within the heart wall and along the course of the coronary arteries may be palpable. Occasionally a thin-walled portion of the left ventricle will paradoxically balloon out with each ventricular systole. Such a phenomenon is always indicative of a myocardial aneurysm, usually due to an old infarct.

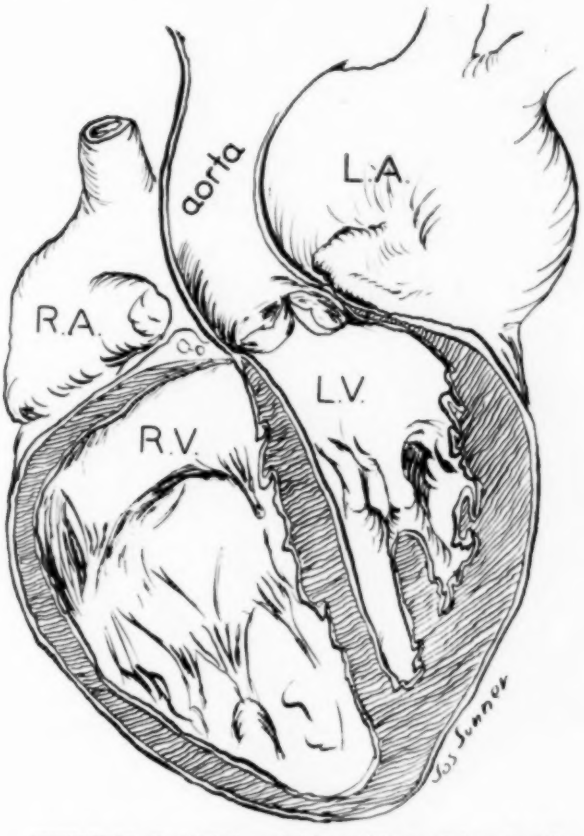

FIGURE 12: Small left ventricle and large atrium found in mitral stenosis.

Disease of the coronary arteries may be recognized by visualization and palpation. Abnormal thickening, tortuosity and calcification may be recognized. Sometimes a definite obliteration of the vessel at a given point is visible.

Generalized dilatation of the aorta is usually related to arteriosclerosis or hypertension. It may be associated with aortic regurgitation especially of the luetic type. Localized dilatation of the aorta is usually due to an aneurysm. Fusiform dilatation of the first part of the aorta with a constriction at the myocardial junction is seen in the rare case of congenital aortic stenosis with fusion of the valve cusps into a tiny cone, similar to the condition seen in congenital stenosis of the pulmonary valve.

In sub-aortic stenosis the aorta is about of normal size, and presents a systolic thrill over its substance. This thrill, unlike that of aortic valvular stenosis, is not limited to the vessel, but can also often be felt in the upper outflow tract of the left ventricle.

(3) Exploration of the interior of the cardiac chambers and adjacent great vessels may be carried out either by inserting a probe, sound, or other small instrument through the heart or

FIGURE 13: Diastolic thrill localized over a point on the left ventricular apex, diagnostic of mitral stenosis.

vessel wall into the vascular lumen, or by inserting a finger into the blood-containing chamber. The latter is far more satisfactory when feasible, since the sense of direct touch may simultaneously be utilized (Figure 15).

One might think, logically, that by simply inserting a finger into one or both auricles by way of the easily tied off appendages that the interior of the respective auricle, the septum, the entrance of the afferent veins (venae cavae or pulmonary veins) and the condition of the respective auriculo-ventricular valve could be ascertained easily and with safety. This assumption is fully justified by practical experience (Figures 16a and 16b).

One might think further that by simply passing the exploring finger through the auriculo-ventricular valve the respective ventricle could be satisfactorily explored. That assumption is for practical reasons unsound. First, any degree of stenosis of the valve would preclude long digital tamponade of the orifice because of dangerous interference with blood flow. Second, the usual left sided approach used in most cardiac operations precludes a very satisfactory exploration of the right ventricle by way of the right

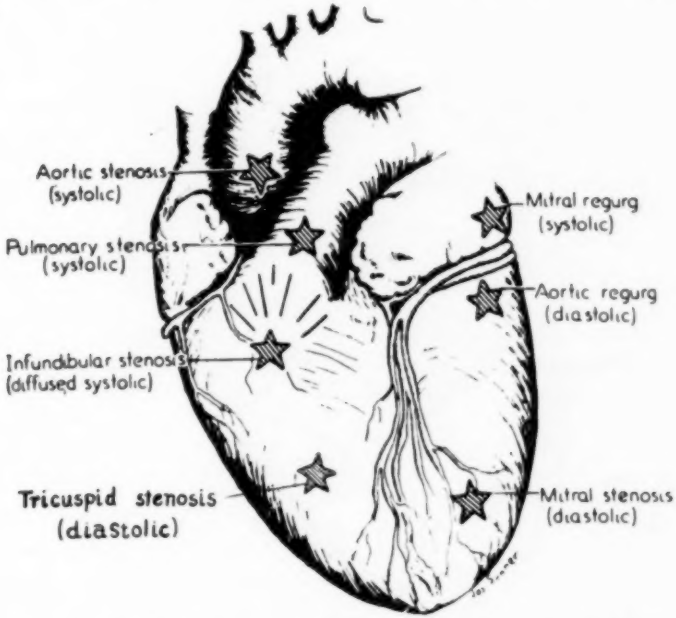

FIGURE 14: Typical locations of thrills felt over the surface of the heart in certain valvular abnormalities.

auricle. Third, the left ventricular outflow tract cannot be well explored in the human adult by way of the mitral valve without danger of tearing the septal cusp.

One might then suggest that the instrument or finger be inserted directly through the respective ventricular wall to explore the appropriate auriculo-ventricular valve, the efferent semilunar valve, the ventricular septum and any masses or obstructions in the ventricular chamber. As far as the right ventricle is concerned this is essentially sound and satisfactory. But digital invasion of the left ventricular cavity, via its myocardial wall is a very formidable undertaking, carrying as it does, considerable danger of ventricular arrhythmia, of major coronary vascular injury, and of possible inability to secure adequate hemostasis after removal of the finger from the heart wall. It must further be appreciated that the left ventricle is the cardiac chamber most directly concerned with the actual maintenance of life itself. Any appreciable or prolonged interference with its function, even if rather tran-

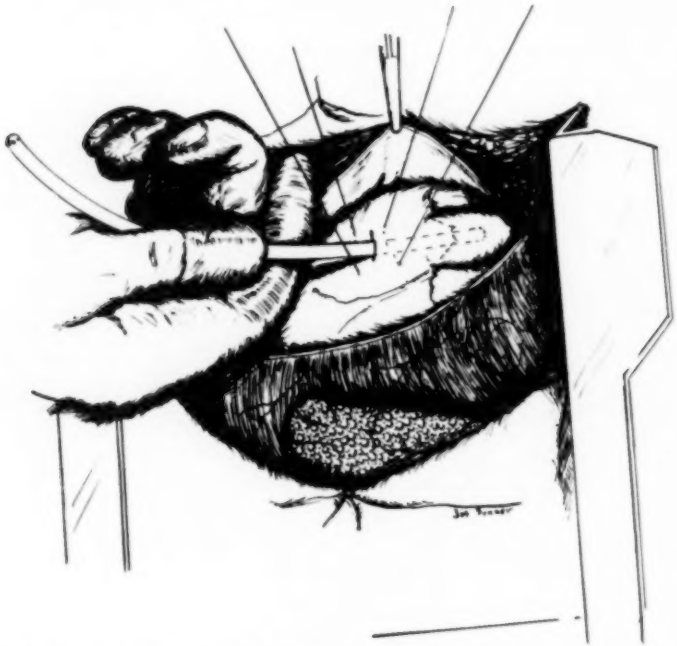

FIGURE 15: Exploration of the interior of the heart and great vessels by direct insertion of a probe or sound through the myocardium. (This illustration demonstrates exploration of the stenotic pulmonary valve).

sient, will lead to prompt falling off of cardiac output, and perhaps to immediate death (Figure 17).

For very practical reasons—the usual left sided thoracic approach inhibiting free exploration by way of the right auricular appendage, and the left ventricle's intolerance to insult, we have come to accept direct digital or instrumental invasion of only two of the cardiac chambers—the left auricle and the right ventricle—as our routine exploration of the interior of the heart. Indeed, the vast majority of intracardiac abnormalities which are not diagnosable by standard preoperative circulatory studies and the first two phases of operative cardiac exploration (pericardial and epicardial) can be definitely catalogued by digital palpation of the interior of the left auricle and of the right ventricle. This is not to be construed as implying that both of these chambers are to be invaded in all cases of routine exploration. For obvious reasons, the chamber will first be chosen which from the totality of existing knowledge of that particular case is more likely to afford the desired pertinent information. Only if such information is not so obtained will the other chamber then be investigated.

The exploration of the left auricle is carried out by inserting the right index finger through an incision in the tip of the left auricular appendage, after applying a hemostatic purse-string suture at its base. It is believed that Souttar[1] was the first to use this approach. This maneuver can be carried out with practically no loss of blood and with no disturbance of cardiac rhythm. The finger can readily recognize an intra-auricular clot or tumor. The orifices of the pulmonary veins are easily located and even counted. The auricular septum can be palpated (except in cases of extreme auricular dilatation) and the foramen ovale located. Any auricular septal defect may, with a little experience, be recognized and evaluated as to size and type (persistent ostium primum or true auricular septal defect). The mitral valve can be palpated and digitally traversed. Its structure and size are estimated with especial reference to possible rheumatic stenosis. It is determined whether mitral regurgitation exists. Even a minor degree of mitral regurgitation (less than 5 cc. per beat) is recognizable by palpation of the rhythmic violent systolic jet of blood from the ventricle.

By passing the finger through the valve into the ventricle, it is possible to feel chordae tendineae, papillary muscles and the left aspect of the lower ventricular septum. It might be possible to recognize a low interventricular septal defect by digital palpation, but the authors have not yet been able to do so. The fact that the pressure differential between the two ventricles directs the abnormal flow from left to right in this defect (when it exists alone) would militate against easy palpatory recognition of a

ventricular septal defect from the left side. The left ventricular outflow tract cannot be safely palpated by the left trans-auricular route, mainly because of danger of tearing the mitral septal (medial) cusp or some of its supporting chordae tendineae. A lesser, but still serious risk, is related to obstruction of the left auriculo-ventricular blood flow especially where some degree of mitral stenosis exists.

In cases where the left auricular appendage is thrombosed, exploration via this route is felt to be generally contra-indicated, except when there is an uninvolved portion at the base of the appendage. However, we have occasionally burrowed or tunnelled with the finger through or alongside a well organized clot to enter the auricular cavity with impunity. We have also produced hemiplegia in a few instances where this technique has resulted in

FIGURE 16a: Digital exploration of right auricle and tricuspid valve via right auricular appendage.

releasing bits of poorly attached thrombus into the circulation. The frequent recognition of soft, eel-like streamers of thrombi floating freely nearby in the left auricle, and only attached in the region of the appendage suggests the advisability of utilizing a different approach to the chamber of the auricle whenever possible.

Two other approaches suggest themselves: (a) direct entrance through the auricular wall, and (b) entrance through a dilated pulmonary vein (Figures 18a and 18b). The former approach is apparently feasible and has been used without untoward incident on several occasions. However, should the auricular wall happen to be friable in any specific case, hemostatic suturing might not be possible. For this reason we have generally chosen to approach the partially clotted auricular cavity by way of the left superior pulmonary vein (Figure 19). This is especially suitable when it is dilated by the hypertension of mitral stenosis—the usual cause of auricular thrombosis.

A purse-string suture should be placed around the base of the dilated vein, and it should be freed up for its full intrapericardial length. Narrow bladed, non-crushing vascular clamps, such as

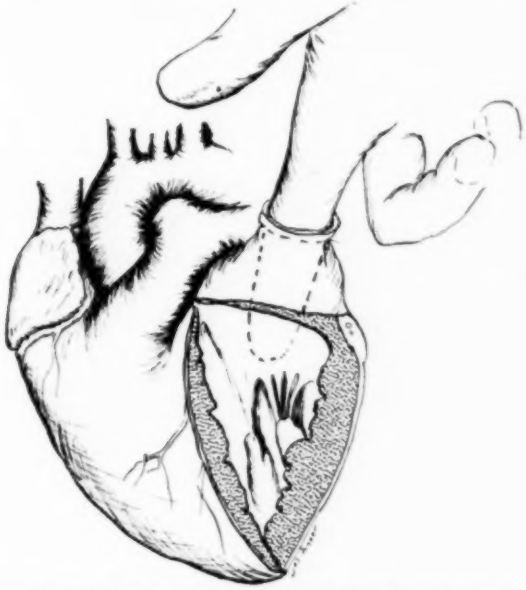

FIGURE 16b: Digital exploration of left auricle and mitral valve via left auricular appendage.

those developed by Potts are applied across either extremity of the mobilized vessel and a *longitudinal* incision is made on its anterior aspect. When the vein incision is long enough, the exploring doubly gloved right index finger is placed between the lips of the incision. As the proximal clamp is removed, the finger is deftly insinuated into the auricle. If the venous incision is in-

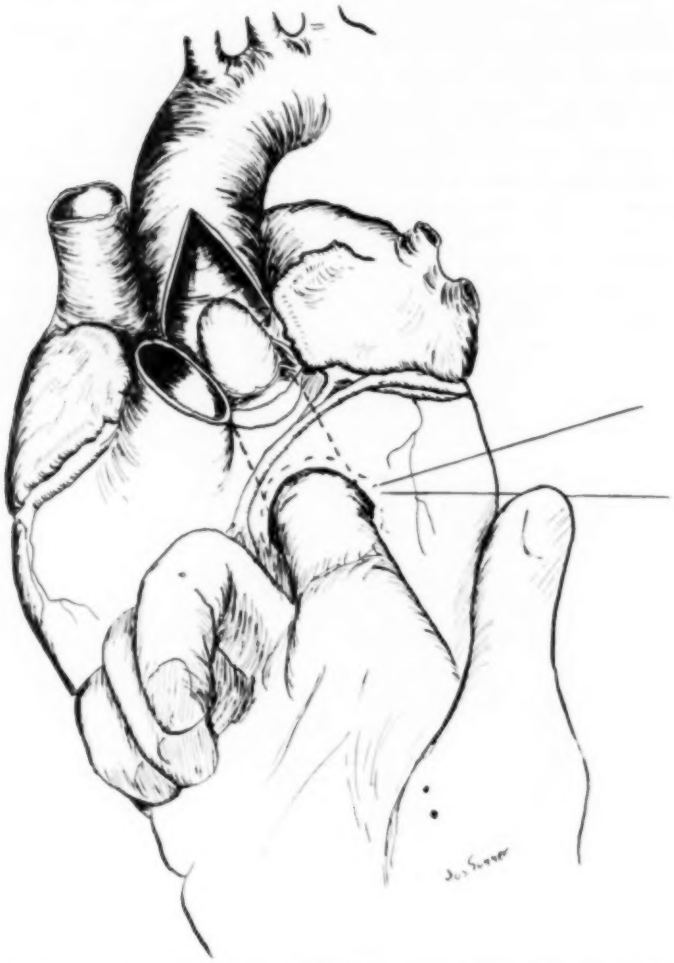

FIGURE 17: Digital exploration of the left ventricle directly via the ventricular wall. This is an extremely dangerous maneuver, rarely justified.

adequate it may readily be elongated, usually toward or actually into the auricle. If the opening is too large, the purse-string will be tightened sufficiently to provide hemostasis. If a flat operating instrument is to be incorporated with the finger, it can be added after completion of the preliminary exploration by partially, but not completely, withdrawing the finger from the vein, until the tipless outer glove-finger is fully exposed. The flat instrument is placed under this rubber sheath and the finger is then re-introduced into the heart.

Such insertion of the finger into the heart by way of the superior pulmonary vein permits determination of the safety of left auricular appendectomy by recognizing whether any clot, extending into the auricle, would be cut off from its base of attachment by this procedure. It also affords the opportunity for mobilization and delivery of any benign pedunculated tumor from the left auricle by forcing it into the base of the appendage from within. As soon as the appendage tip is opened, the mass can then be forcefully extruded. Pedunculated clots within the auricle can be (and have been) evacuated in a similar manner.

Exploration Directly Through the Wall of the Right Ventricle

Exploration of the right ventricle by way of an incision directly through its anterior wall is amazingly satisfactory. It was first

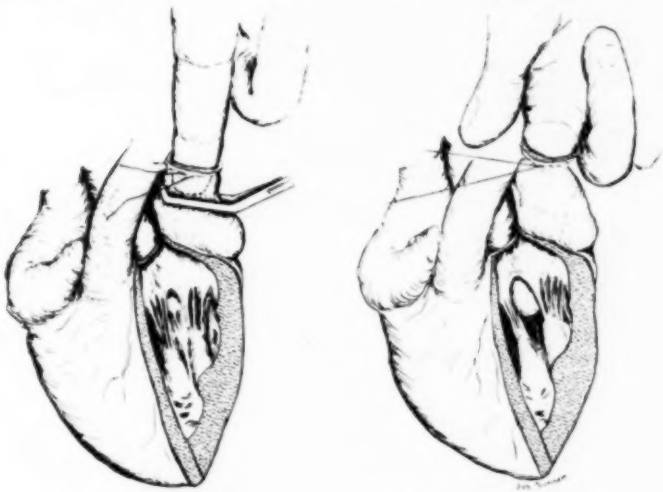

FIGURE 18a FIGURE 18b

Figure 18a and b): Technique of digital exploration of left auricle and left side of heart via left auricular appendage.

proposed and performed by Brock[2] in the exploration of the ventricular outflow tract for pulmonic stenosis. Since then it has been so employed by Dr. Alfred Blalock[3] and others.[4] The authors have used it for this purpose and for certain others, as will become immediately apparent.[5-8] At this point it must be clearly emphasized that the finger is far too large an instrument to insert into the right ventricle of very small infants. In them, a probe or small urethral sound may be inserted through the ventricular wall in the same way and for the same purposes. Of course, one then has the handicap of being without direct "tactile vision" of the interior of the ventricle, but much information may nevertheless be thus obtained.

In children the little finger of the left hand is usually chosen, but in larger persons the more adept left index finger is the preferable exploring instrument. By this digital exploration the entire ventricular septum can be studied for defects, high or low, abnormal papillary or infundibular protrusions, and for the presence of tumors, clots or vegetations.

It is particularly easy to recognize ventricular septal defects

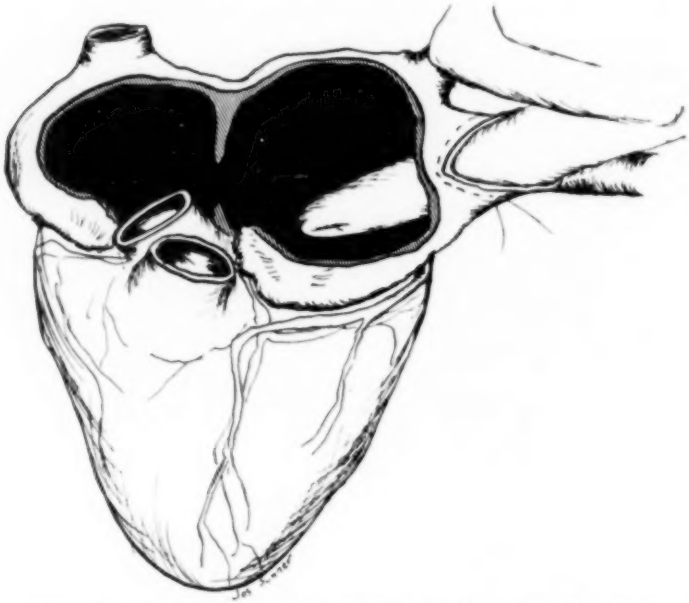

FIGURE 19: Digital exploration of left side of heart via dilated left superior pulmonary vein. This is one of the practical approaches for digital exploration of the interior of the heart.

with a left to right shunt since the systolic jet of blood from the higher pressure left ventricle is unmistakable. In right to left shunts the defect is nearly always high in the membranous septum and in a characteristic location—to the right of the pulmonary outflow tract, and just below the aortic valve cusps. Knowing this probable location it is not difficult to pass a finger into and through the defect, even when there is a right to left shunt.

The right ventricular outflow tract, the pulmonary valve and artery may be evaluated for constrictions, general stenosis or for abnormally large size. It may be possible to detect the orifice of an aortic septal defect by palpating the systolic jet from the high pressure aorta into the pulmonary artery.

An infundibular stenosis or obstruction is most readily recognized by the exploring finger, and can usually be accurately evaluated as to type (muscular, membranous, fibrotic), location (subvalvular, high, low) and size and location of the tiny aperture.

The auriculo-ventricular (tricuspid) valve is easily recognized.

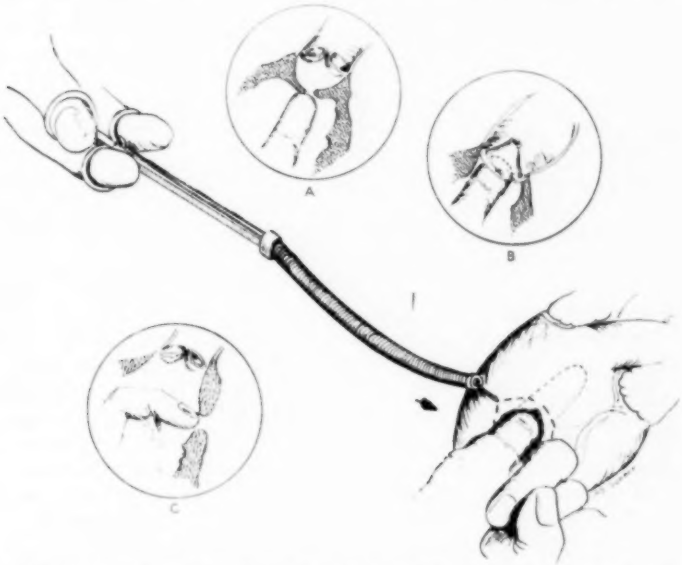

FIGURE 20: Digital exploration of the right side of the heart via the right ventricular wall. This is another practical approach to the interior of the heart. A Rumel-Belmont tourniquet is used to control bleeding.

Inserts: (a) Exploration of infundibular septum.
(b) Exploration of congenitally fused pulmonary valve.
(c) Exploration of ventricular septal defect.

Abnormally low attachment (Ebstein's Disease) of the valve within the ventricle, stenosis or regurgitation are easily determined. The exploring finger can be easily passed through the normal tricuspid valve to palpate the interior of the right auricle. Auricular septal defects may be diagnosed in this manner. The large size of the normal tricuspid aperture makes it unlikely that the valve orifice will be significantly obstructed during the period of transvalvular digital exploration.

In the actual performance of such right ventricular transmyocardial investigation the operator will be guided in the location of his incision into the heart, first by the pathology suspected or searched for, second by the coronary arterial pattern, and third, by the thickness of the right ventricular myocardium. The first two considerations are obvious ones. An incision in the apex of the right ventricle would be most unsuitable if a high ventricular septal defect were suspected. Transection of a major coronary artery in making the incision would be most unsurgical and possibly disastrous. The third consideration is related to the occasional presence of a thin-walled infundibular chamber above an infundibular stenosis or septum. Such a chamber may not be sufficiently tough-walled to withstand placement and tying of hemostatic sutures. It can, however, always be recognized by preliminary inspection or palpation of the intact heart surface; usually by both.

It is possible to insert a finger through a small incision in the right ventricle without any hemostatic control other than the tonus of the myocardium. After removal of the finger satisfactory suture of the opening is usually possible.

The Brock method of use of stay sutures in either lip of the myocardial wound is probably safer, since hemostasis is more certainly accomplished both during definitive exploration and during the repair by simply crossing the sutures over the wound.

By far the most dependable technique, however, is the application of a definite purse-string of heavy silk deep into the myocardial wall, and the use of a Rumel-Belmont tourniquet (Figure 20) to control the tension. The incision is then made in the portion of myocardium included by this suture, and the finger is slipped through it into the ventricular chamber. The order of exploration will vary with the nature of the pathology expected and found. But it should be methodical and complete if the patient's condition justifies more than simple identification of the primary lesion, correction, if possible, and termination of the procedure. Repair of the cardiac incision is by interrupted sutures during temporary hemostasis maintained by tightening the purse-string suture.

Even though a left thoracic incision, anterolateral or lateral

is usually employed in cardiac exploration or surgery, it is possible, although somewhat inconvenient technically to digitally explore the right auricle through the right appendage. The right index finger seems most satisfactory, permitting "digital visualization" of the auricular septum, the venae cavae and the tricuspid valve. Digital or incisional enlargement of a stenotic tricuspid valve can thus be accomplished.

Actual Cases Illustrative of the Three Phases of Cardiac Exploration

First Phase

Case 1: J.D. (2994). A five year old white girl admitted to Hahnemann Hospital, Philadelphia, on November 10, 1947 because of shortness of breath and mild cyanosis since one year of age. R.B.C. 4.1 - 5.1 million. Hemoglobin 13.7 - 16.8 gm. The left precordium bulged forward abnormally. There was a harsh Grade III systolic murmur and thrill over the precordium most prominent over the fourth left interspace. The apex beat was palpable in the left anterior axillary line, sixth interspace.

X-ray film and fluoroscopy revealed a prominent pulmonary conus and dilated pulmonary arteries. The heart was definitely enlarged, especially the right ventricle.

Exploratory operation was performed on November 24, 1947. Direct water manometric determination of pressure in the pulmonary artery was 673 mm. water. This was considered evidence of an adequate pulmonary blood flow and confirmatory of the suspicion of Eisenmenger's syndrome. It was felt that a shunt (Blalock-Taussig or Potts) operation would not improve blood oxygenation and would only add to the cardiac work load.

The operation was, therefore, terminated at this point, the pericardium never having been opened. Convalescence was uneventful and the child is still living a restricted life.

Second Phase

Case 2: J.R. (53526). A six year old white boy was admitted to Hahnemann Hospital on March 27, 1951. There was a harsh Grade III systolic murmur and accompanying thrill, maximal over the second left intercostal space near the sternum. The murmur was transmitted through to the back.

The pulmonary artery was shown by fluoroscopy to be dilated and to pulsate violently. There was no cyanosis nor dyspnea. R.B.C. 4.2 million with 12.9 gm. hemoglobin. No precordial enlargement. An atypical patent ductus was suspected.

Exploratory operation was performed on April 2, 1951. A large patent ductus arteriosus was exposed, divided and sutured. However, a systolic thrill was still palpable over the large prominent pulmonary artery. Opening of the pericardium revealed a greatly dilated pulmonary artery with a constriction at its origin. A typical jet-like localization of the beginning of the thrill indicated valvular pulmonic stenosis. The chest wall incision was extended anteriorly and a direct transventricular Brock type of valvulotomy was performed to relieve the pulmonic stenosis. The

thrill in the artery immediately became more widespread and coarser, and the dilated but previously somewhat flaccid vessel became turgid, indicative of increased blood flow. Convalescence was uneventful.

Case 3: J.M. (29093). An 11 year old white male was admitted to Hahnemann Hospital on August 2, 1949. He presented no evident cardiac enlargement. There was a rough Grade III systolic murmur without a thrill best heard in the second left interspace, near the sternum. Two years previously this had been described as being "machinery" in type. There was no cyanosis. The child was well developed, even somewhat obese. R.B.C. 4.1 million; Hgb. 12.1 gm.

Pulmonary vascular markings were normal but the pulmonary conus was greatly dilated. Aortography failed to reveal a patent ductus arteriosus.

Exploration was performed on August 8, 1949, and a patent ductus 1 cm. long and 3.5 mm. is diameter was divided and sutured. A systolic thrill limited to the beginning of the pulmonary artery was still palpable after division of the ductus. The pericardium was opened. It was conjectured that there probably existed a high ventricular septal defect for which we at that time had no surgical treatment to offer.

Convalescence was uneventful except for retained bronchial secretions which necessitated bronchoscopy. This patient will be readmitted for re-evaluation and possible surgical intervention in the near future.

Third Phase

Case 4: R.T. (42242). An 18 year old white female was admitted to Hahnemann Hospital on June 19, 1950. She was known to have had a heart murmur since infancy. She had always been kept on restricted activity. There was no cyanosis or precordial deformity.

A rough Grade III systolic murmur was heard best along the left border of the sternum in the second and third interspace. There was no audible diastolic murmur. The pulmonic second sound was accentuated three plus. Aortography revealed no ductus. The heart was slightly enlarged and the pulmonary vascular markings were increased.

Exploratory operation was undertaken on June 23, 1950. A long obliterated ligamentum arteriosum was found. It had no visible lumen when divided. There was a palpable systolic thrill over the base of the right ventricle. A small opening was made in the anterior ventricular wall in this region, and a No. 18 urethral sound was passed through it into the ventricular cavity. By instrumental palpation a high ventricular septal defect was found in the membranous septum. Since a ventricular septal defect had not been corrected up to that time, nothing further was done. Recovery was uneventful except for the development of penicillin rash. Perhaps subsequent definitive surgery should be undertaken.

Case 5: J.M. (58025). A 17-month old white male admitted to Hahnemann Hospital on July 9, 1951, acyanotic, with a systolic thrill over third left interspace and a loud harsh systolic murmur with a diastolic component in the same area. Heart enlarged two plus. (R.V., L.V., P.A. and hilar vessels). ECG revealed N.S.R. with some degree of left ventricle enlargement.

The case was considered to be one of atypical patent ductus arteriosus. Exploratory operation was carried out on July 12, 1951. A patent ductus 1 cm. long and 5 mm. in diameter was divided and sutured. However, the

lumen was seen to be only about 1 mm. in diameter. The systolic thrill in the pulmonary artery persisted after division of the ductus. The pericardium was opened and the pulmonary artery was seen to be large but not constricted at its origin as in pulmonic stenosis. It was thought that an aortic septal defect might be present. Therefore, a No. 16 urethral sound was inserted through a small incision guarded by a purse-string suture in the anterior wall of the main pulmonary artery. Careful instrumental palpation over the entire area of common aortic and pulmonary wall failed to reveal an aortic septal defect. The case was considered to be probably one of a high interventricular septal defect. Because of the very small size of the infant and commensurate small heart, it was deemed wisest to attempt no surgical correction at this time. Recovery from operation was uneventful.

Case 6: M.D. A 33 year old white female was referred to Hahnemann Hospital on September 7, 1950, with a diagnosis established at a very eminent clinic of mitral stenosis. This was confirmed by clinical examination and phonocardiograph at our own clinic. There was no history of previous rheumatic infection. There was a classical diastolic murmur with presystolic accentuation. Pulmonary edema and hemoptysis were prominent in her history.

On September 14, 1950, operation was undertaken with the diagnosis of "pure" mitral stenosis. A finger inserted into the left auricular appendage found a normal mitral valve partially obstructed by a soft pear-shaped tumor arising from the auricular septum. This was enucleated from its attachment to the septum but proved too large for easy evacuation through the incision in the appendage. Considerable force was applied resulting in partial morcellation of the tumor, and in its evacuation. The condition of the heart improved and it appeared that all would be well. However, during the closure of the chest, the auricular wall, which presumably had been damaged during the removal of the tumor became ruptured at the base of the appendage. Death resulted from exsanguination.

Case 7: M.L. (44449). A 29 year old white female nurse was admitted to Hahnemann Hospital on August 16, 1950, with the diagnosis of mitral valve disease. Progressive dyspnea and evidences of congestive heart failure were the chief complaints. There was no cyanosis. The heart was moderately enlarged, predominantly the right ventricle and its outflow tract. The pulmonary artery and conus segment were greatly enlarged. R.B.C. 4,450,000; Hbg. 13.7 gms.

Cardiac catheterization was performed on August 19, 1950. The catheter passed readily from the right to the left auricle and into the pulmonary veins, proving the existence of an auricular septal defect.

At operation on August 25, 1950, the operator's right index finger inserted through the left auricular appendage readily recognized not one but two defects in the auricular septum. One was too small to admit the finger tip and was located about in the usual location of the foramen ovale. The other was a much larger persistent ostium primum.

Using the intracardiac finger as a guide the operator passed a threaded curved probe through the tip of the left auricular appendage, through the persistent ostium primum and out through the tip of the right auricular appendage. The appendages were then both invaginated by a modification of Swan's technique to become tightly apposed in the defect.

While this technique cannot completely close a persistent ostium primum, it can greatly reduce the amount of left to right shunt.

Convalescence was nearly uneventful, and the patient has since been able to return to full duty as on operating room nurse. Her evidences of congestive failure have not returned, even though digitalis therapy has been discontinued.

Case 8: R.H. (54320). A 40 year old white male was admitted to the Hahnemann Hospital on April 13, 1951. He had been known to have heart murmurs for 21 years. For two years prior to admission he had been receiving digitalis and diuretic therapy because of recurrent evidences of congestive failure. He had a normal sinus rhythm, normal blood pressure and a moderately enlarged heart. In the aortic area there was a Grade III harsh systolic murmur transmitted up the neck, with an associated localized systolic thrill. There was a diminished aortic second sound. In the third and fourth interspaces at the sternal margin there was a high-pitched blowing early decrescendo diastolic murmur. In the mitral area was heard a loud sharp first sound with a short moderately harsh Grade II systolic murmur. Also there was a short presystolic murmur crescendo in type.

It was agreed that he had rheumatic deformity of both the mitral and aortic valves, but it was uncertain which was the more important clinically. It was decided that he should be explored through a left anterior thoracic incision. The mitral valve would be explored first and corrected if necessary. The aortic would only be attacked if the mitral deformity seemed insufficient to account for the clinical impairment.

On April 25, 1951, the left fourth intercostal space was widely opened anteriorly. The pericardium was incised anterior to the left phrenic nerve. A purse-string ligature was placed about the base of the left auricular appendage. The right index finger was inserted through an incision in its tip. The mitral valve was found to be somewhat thickened, but the orifice was capable of admitting two fingers, and there was only very slight regurgitation. It was deemed unnecessary to do anything to this valve which was evidently not responsible for the clinical symptoms. Therefore, the appendage was ligated and oversewn.

The root of the aorta was palpated disclosing a harsh systolic thrill at the valve level, with a localized palpable jet on the right side of the aorta just above the valve. A special curved aortic dilator was inserted through the apex of the left ventricle, was passed up along the ventricular septum and finally through the aortic valve. It was vigorously dilated and then the instrument was closed and withdrawn. The small opening in the left ventricle was closed by a purse-string suture and was oversewn.

The condition of the patient was satisfactory for a few hours, and then became precarious as evidences of intrathoracic bleeding became apparent. The wound was reopened in the operating room and it was determined that the bleeding was from the left ventricular wound. This was resutured with mattress sutures and the patient was vigorously transfused. Recovery then was uneventful and he has since been able to return to work.

Case 9: G.W. (50939). A 26 year old white male was admitted to Hahnemann Hospital on January 29, 1951. He had been known to have a heart murmur since the age of 16 and had been kept on restricted activity ever since. He had had a classical attack of rheumatic fever in 1945. At

the time of admission there was no cyanosis, edema nor dyspnea. Sinus rhythm existed. The heart was not enlarged beyond normal limits but angiocardiography on February 2, 1951 revealed a suggestion of slight enlargement of the right ventricle. There was a long harsh Grade III systolic murmur heard best in the mid-sternal area, level of the third interspace.

On February 6, 1951, exploration was carried out through a left anterior thoracic incision (third interspace). A harsh systolic thrill was palpable in the region of the right ventricular outflow tract. It was not well transmitted up the pulmonary artery. Two stay sutures were placed in the anterior wall of the right ventricle about an inch below the pulmonary valve. A 2 cm. incision was made in the myocardial wall between the stay sutures and the operator's left index finger was inserted in the right ventricular cavity. It was easy to pass the finger up through the roomy pulmonary valve and thus to demonstrate its adequacy. Palpation of the membranous septum just below the level of the aortic valve revealed a small high ventricular septal defect. This was indicated by a rhythmic systolic jet of blood escaping through it from the left ventricle. A threaded curved probe was passed along the intracardiac finger, was guided by it through the septal defect and was brought out through the anterior wall of the left ventricle not far from the septum. The sutures were grasped and the probe was withdrawn. The sutures were then used to draw the free end of a pedicled pericardial graft completely through the right ventricle, through the septal defect, and out through the anterior wall of the left ventricle. This tubular graft effectively "corked" or plugged the ventricular septal opening, shutting off the systolic jet and thrill much as though a faucet had been turned off.

Recovery has been uneventful. He still presents a very slight systolic murmur.

SUMMARY

Exploratory surgery of the heart is logical, simple, and when performed along the lines indicated, a relatively safe procedure. In most cases, fortunately, it not only establishes the anatomical diagnosis but permits the prompt carrying out of corrective operative measures.

In the last analysis, it has always been, and always will be the final diagnostic or confirmative measure in all cases subjected to major cardiovascular surgery.

RESUMEN

La cirugía exploradora del corazón es lógica, sensilla, y cuando se realiza de acuerdo con los lineamientos indicados, resulta ser un procedimiento relativamente seguro. En la mayoría de los casos, afortunadamente, no solo se establece el diagnóstico anatómico, sino que se permite la pronta aplicación de las medidas optratorias correctivas.

En último análisis, siempre ha sido y será la medida diagnóstica final, o la confirmativa, en todos los casos sujetos a cirugía cardiovascular.

RESUME

La chirurgie exploratrice du coeur est logique, simple et relativement sans danger, lorsqu'elle est pratiquée selon les indications normales. Dans la plupart des cas, heureusement elle permet non seulement de préciser le diagnostic anatomique, mais aussi de mettre en oeuvre l'opération corrective.

En dernière analyse, la chirurgie exploratrice a toujours permis et permettra toujours le diagnostic précis dans tous les cas susceptibles d'être traités par la grande chirurgie cardio-vasculaire.

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The Recognition of Nonallergic Asthma*

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In the past several years an increasing number of patients have been referred for allergy surveys. Most of these individuals are really allergic, and for them we plan and carry out an extensive examination, including skin tests and other techniques based on allergy.

Some of these patients, however, are not allergic. Among these are some who wheeze and are short of breath from conditions which simulate true bronchial asthma. Let us discuss a few of these patients who have what we may call "nonallergic asthma."

Case 1: B.A., age 15. This girl was referred July 17, 1950, because of "asthma." She had bronchitis at nine, with severe "cold" and cough. For the past three months "bronchitis" has recurred again and again, as shown by dyspnea, orthopnea, cough, rattling in the chest and wheezing. Ten days ago her "asthma" suddenly became violent and she was in a hospital for two days, with relief after oxygen and intravenous fluids. Adrenalin was not given. There was no nasal symptom but the girl had lost 15 pounds in one month.

She was worse at night and after exertion and received little benefit from Pyribenzamine and ephedrine. Her past history revealed pneumonia, scarlet fever, mumps and chicken pox, and removal of tonsils and adenoids. The family history was negative for allergy. The urine, Kahn test, blood and sputum were negative, with 3 per cent eosinophils in the blood and none in the sputum.

Examination revealed a well-nourished white girl with no dyspnea at that time. Resonance was good over both lungs, but breath sounds were almost entirely absent on the right side, especially the lower two-thirds. The other lung was normal, and wheezing was absent. The heart was not displaced, and the examination was otherwise negative. On fluoroscopy, the excursion on the right side was diminished, and x-ray films (Figures 1 and 2) showed very little. We did notice that inspiratory sounds on the right side were a little rougher than those on expiration.

We therefore concluded that her dyspnea and wheezing and the almost complete absence of breath sounds on the right side must be due to an obstruction of the right primary bronchus. Because she was only 15 the diagnosis of a bronchus adenoma suggested itself.

The first bronchoscopic examination (Dr. Jerome Head) revealed a "normal larynx and trachea. About half-way to the carina, a tumor mass was found projecting from the right lateral wall of the trachea, partially obstructing the lumen. Pieces were secured for microscopic study and in

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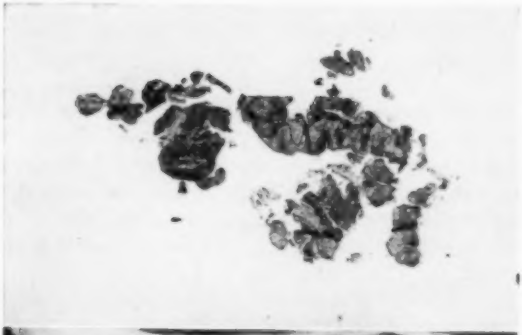

FIGURE 5

FIGURE 4

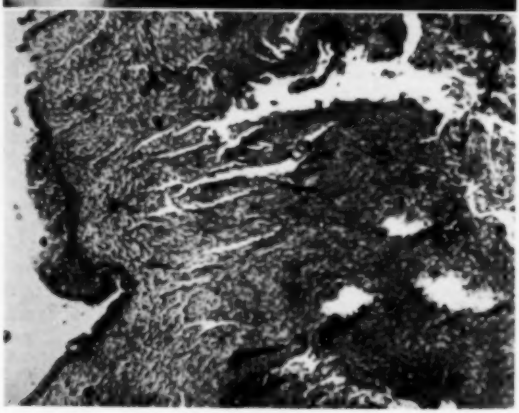

FIGURE 3

the process there was free bleeding." One week later more tumor tissue was removed, and on the third week the rest was removed through the bronchoscope or was coughed up; one chunk was as large as the end of her thumb. A week later re-examination showed that the tumor was gone though the remainder of the pedicle was seen to come from an elongated patch 5 x 10 mm. The carina was markedly widened and looked inflamed.

Tissue examination (Figure 3) established the fact that the tumor was a leiomyoma rather than an adenoma. This has a tendency to recur and already there has been a slight reappearance of the mass. Her so-called "asthma," however, has disappeared. Skin tests, of course, were not carried out as there was no evidence of allergy.

Case 2: Mrs. J.C., age 41, entered Wesley Memorial Hospital June 23, 1946, with so-called "asthma" for about four months. The wheezing and dsypnea became progressively worse, and vomiting and slight fever were also present. She was known to have had a carcinoma of the uterus and vagina for the past six years, with apparent quiescence after intensive radiotherapy. She was moderately nourished and had considerable dyspnea, wheezing and orthopnea; epinephrine and aminophylline gave some relief. On standing in front of the patient, and without the use of a stethoscope, we noted that the wheezing was more marked on inspiration and that it really constituted a stridorous type of breathing. This fact at once ruled out the diagnosis of bronchial asthma, in which, of course, wheezing and dyspnea are almost always more marked on expiration. We abandoned the diagnosis of true allergic asthma despite the fact that successive examinations of the sputum showed that 2, 80 and 100 per cent of the cells were eosinophils.

Our diagnosis was necessarily an obstructive lesion in the larynx or trachea. Laryngoscopy was normal, but on bronchoscopy the carina was very broad and bulged into the bronchi, and was so swollen that only a narrow slit was visible at the entrance to the right main bronchus, and a small round opening on the left side. The tissue was firm and red but

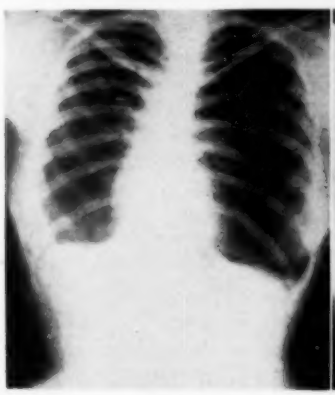

FIGURE 1

FIGURE 2

did not bleed. Two pieces were removed, with the diagnosis of squamous celled carcinoma. We were unable to save her life (Figures 4 and 5).

Case 3: Mrs. D.G., white, age 81, was seen at Cook County Hospital. "Bronchial asthma" was the admitting diagnosis, and some relief was obtained from aminophylline and epinephrine. Her wheezing and dyspnea, however, were also more marked on inspiration, and stridor could be clearly heard without a stethoscope. Percussion showed marked dullness in the right upper chest, and the x-ray film (Figure 6) revealed a large mass. Because of her age and general good condition and lack of any other findings, the diagnosis of a large substernal goiter seemed logical. Surgery was advised but was refused. She went home with her dyspnea and wheezing and returned a year later, with death from terminal broncho-pneumonia. Autopsy revealed a huge colloid goiter which had grown around the trachea and which compressed the right primary bronchus. It could have been completely removed.

Case 4: Mrs. O.C., Negro, age 35, proved intensely interesting and she was the subject of a recent clinico-pathological conference at Wesley Memorial Hospital. She was admitted wheezing and gasping for breath at midnight, January 4, 1951, via ambulance. She could not lie down, and her ankles and legs were very edematous. The heart was dilated, and the liver was palpated 3 cm. below the costal arch.

She had been well until five years previous to admission. She went to a clinic because of dyspnea on exertion and epigastric pains. The findings at that time were not remarkable, but x-ray films showed an infiltrating process in both lung fields. At that time she had some ankle edema after prolonged standing or walking. The diagnosis of Boeck's sarcoid was strongly considered. Later she went to two other clinics and was told, according to the patient, that she had a rare type of bronchial asthma.

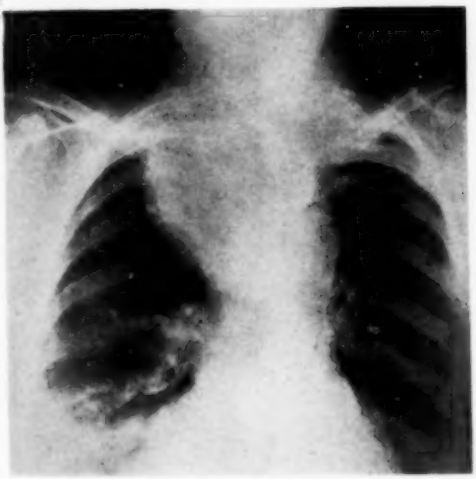

FIGURE 6

One year ago she had bronchopneumonia, with gradual recovery, but wheezing persisted.

At the hospital on this admission, urinalysis revealed 10 mg. albumin per 100 cc. There were 3,700,000 erythrocytes and 5,500 leucocytes, including 1 per cent eosinophils. Three sputa disclosed 45, 90 and 23 per cent eosinophils, respectively, with no acid-fast bacilli on smears or cultures nor after injection into a guinea pig. The total protein was 6.12 grams, with 2.84 albumin and 3.28 globulin per 100 cc. The nonprotein nitrogen, calcium, phosphorus and alkaline phosphatase were normal. Repeated examinations of sputum and bronchial smears were negative for yeasts, molds and other fungi, and cultures showed some Diplococci pneumoniae and Staphylococcus aureus. Bronchoscopy revealed edematous bronchial mucosa which bled easily but there was no evidence of obstruction. Two skin tests were negative for tuberculosis, and tests were also negative for histoplasmosis, coccidiomycosis, and brucellosis. Stools were also normal. An electrocardiogram showed findings consistent with early right heart strain.

The x-ray films (Figures 7a and 7b) showed the lungs as they were in 1946 and again in 1951. One could see that areas of increased density were scattered throughout both lungs, especially in the middle two-thirds. Pulmonary fibrosis was suggested, and one could see little change in the lungs during the intervening five years. The 1951 film showed that the heart had become much larger.

Treatment on admission consisted chiefly of bed rest, digitoxin, mercuhydrin, and some aminophylline. The edema disappeared and the liver became smaller, but the wheezing, dyspnea and orthopnea persisted, and several attacks of so-called "asthma" occurred from time to time. She went home, but 18 days later she had an acute exacerbation. She was returned to the hospital via ambulance but was dead on arrival.

The diagnosis of this case provoked much discussion. The persistent pulmonary infiltration ruled out bronchial asthma, this despite the

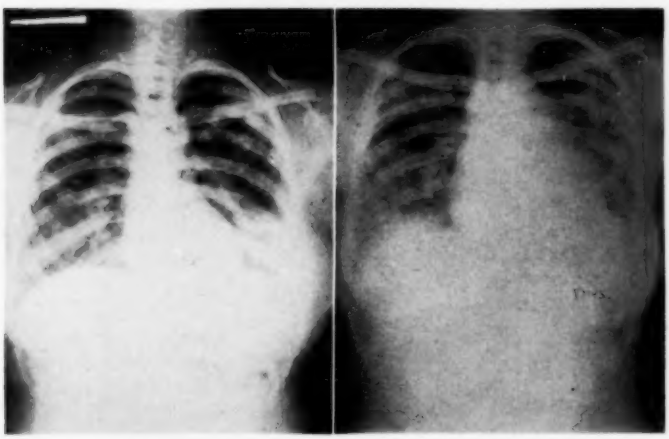

FIGURE 7a FIGURE 7b

FIGURE 9

FIGURE 8

eosinophilia in the sputum. The diagnosis of Boeck's sarcoid was suggested by several, but against this were the facts that there were no x-ray changes in the bones, no skin or eye lesions, no enlargement of the spleen, and not enough reversal of the A-G ratio.

Other conditions were suggested, but questioning of the patient had revealed that she operated a drill press in 1944-1945, and during this time she also worked with a buffing machine which gave off a great deal of dust. Sometimes she wore a mask, sometimes she did not. Because of this exposure and because of the chronicity of the process, it seemed much more likely that she had developed silicosis of the lungs and from this cor pulmonale and resultant right heart failure. This diagnosis was confirmed by the autopsy, at (Figure 8) which the patient was found to have anthracosilicosis of the lungs, spleen and stomach, and of the parabronchial, pancreatic and renal lymph nodes—all this in addition to cor pulmonale and cardiac decompensation.

Case 5: Mr. A.G., age 77. In this case there is illustrated a condition which is frequently and tragically mistaken for bronchial asthma. This man was admitted as an emergency. He came by ambulance because of a sudden and terrific attack of so-called "asthma," and was immediately given an intravenous injection of aminophylline. This was his first attack, and there was no history of allergy in the patient or in his family. This attack began five hours before admission, and there was no complaint of pain.

Examination revealed a moderately nourished, elderly, white male in very acute distress. He was almost moribund, and the so-called "death rattle" was easily heard without a stethoscope. Cyanosis and tachycardia

FIGURE 10

Bronchial Asthma	*Acute Cardiac Dyspnea ("Cardiac Asthma")*
Paroxysmal dyspnea (allergic)	Paroxysmal dyspnea (cardio-renal)
History previous attacks	Attacks very few
Obstruction lower air passages	Pulmonary edema (failure left ventricle)
Onset in early life	Onset after 40, usually
Allergy in patient and family	Hypertension, coronary disease, aortic regurgitation, chronic nephritis
Eosinophilia blood and sputum	Absent
Wheezing, prolonged expiration all over both lungs	Moist rales, especially at bases; some wheezing
Warm perspiration	Cold clammy skin
Condition usually good	Often in shock
Heart usually small	Heart dilated
Pulse good	Pulse often thready, irregular
No fear of death	Fear of death
Epinephrin usually gives relief; morphine dangerous	Morphine best, also digitalis and venesection; epinephrin doubtful
Positive skin tests, usually	Negative
Elimination of cause gives relief, often complete	Rest in bed, etc., prolongs life
Circulation time normal	Circulation time prolonged

FIGURE 13

FIGURE 12

FIGURE 11

were present. There were watery rales all over both lungs. His heart seemed dilated and his blood pressure was 150/90. An occasional wheeze was also heard, and the liver edge was not made out. The lower extremities were not swollen.

The diagnosis was at once changed to "acute cardiac dyspnea" (cardiac asthma, acute suffocative pulmonary edema). He was promptly injected with one-fourth grain morphine and 1 150 grain atropine, repeated in two hours. Oxygen was given by inhalation and digitalis intramuscularly, and we assured the man that he would be much better very quickly. In about 10 minutes he was much better,—he became quiet, there was less rattling, and by evening his dyspnea was almost gone.

We kept him quiet as long as we could, and electrocardiograms showed extensive cardiac damage. After four weeks he signed a release and returned to his work as a printer. We learned that he died some months later. This was to be expected as the prognosis in this type of heart disease is unfavorable. Palmer and White,[1] for example, have shown in a series of 250 patients with cardiac asthma, that 170 are known to have died with an average duration of life of only 1.4 years after the first attack.

There was bilateral passive congestion of the lungs when this patient's left ventricle suddenly dilated during that attack (Figure 9). In Figure 10 is our differential diagnosis between bronchial asthma and acute cardiac dyspnea (cardiac asthma). One notes that bronchial asthma rarely begins after middle age unless the patient has had some previous nasal allergic condition, e.g., nasal polyps or perennial rhinitis or hay fever. When sudden dyspnea, with or without wheezing, first appears after 50, the odds are all in favor of a cardiac rather than an allergic etiology. This differentiation is extremely important as morphine is often life-saving in cardiac emergencies, whereas it may kill a patient who has bronchial asthma. Epinephrine (Adrenalin), on the other hand, almost always helps the true asthmatic, and aminophylline is certainly much more beneficial in bronchial asthma than in cardiac diseases.

Case 6: Miss R.C., age 19, white. This last case illustrates a somewhat controversial subject. She was a billing clerk, and reported at the office October 1, 1949, with asthma and nose trouble—duration, three years. She wheezed, coughed and had some dyspnea especially on exertion. Her nose was blocked a great deal, along with a watery nasal discharge and frequent frontal headaches. There were 11,600 leucocytes, with 11 per cent blood eosinophilia and with 30 per cent eosinophils in the sputum.

Skin tests were carried out by the scratch method, supplemented by intradermal tests. There were many positive skin tests, and as a result she received and is still being given injections for hyposensitization. These consist of extracts of grass pollen, house dust, feathers, molds, flaxseed and kapok.

The interesting and unusual finding in this girl was the presence of clusters of bubbling rales heard below the left clavicle. These rales were heard on every examination, and were typical of those found in sacular bronchiectasis. The first bronchograms failed to visualize the left upper lobe, but on the second attempt the sacular bronchiectasis was beautifully shown (Figures 11, 12 and 13). Bronchoscopy revealed marked constriction of the left main bronchus, as though a gland was pressing on both the upper and lower lobe orifices. The bronchus was dilated twice, and lobectomy was then carried out in June 1950. When the chest

was opened the left upper lobe was found to be congenitally very small and was only as large as a lemon. This lobe was removed, and sections showed the sacular bronchiectasis along with chronic bronchitis and chronic interstitial pneumonitis. There was no tissue eosinophilia. The left lower lobe was quite large and filled most of the left chest cavity.

The patient's progress has been most satisfactory. Her cough and wheezing and frequent bouts of fever have disappeared, although she still has mild rhinitis. There is no further evidence of bronchial asthma, and perhaps her wheezing was chiefly associated with bronchiectasis. We never did hear the generalized wheezing which is so typical of true bronchial asthma.

There is some controversy regarding the relationship of asthma and bronchiectasis. Watson and Kibler,[2] said that 90 per cent of their cases were proved allergic. Mallory,[3] on the other hand, in autopsies of 50 patients who had bronchiectasis, found that emphysema and asthma were not important factors. From my own experience, bronchiectasis is rarely due to bronchial asthma, although the two conditions are rather frequently found in the same person.

I would also like to suggest that the diagnosis of bronchiectasis, if present, be made as early as possible so that lobectomy may be successfully carried out. This girl is one of three of my patients in whom surgery has been very successful. Unfortunately, we have other patients in whom lobectomy cannot be done because they are either too old or too many lobes have been involved.

Discussion

From these cases, seen over many years, one might get the impression that so-called "nonallergic asthma" is common. This is not true. For every case which suggests the diagnosis of asthma, probably 90 per cent have real bronchial asthma and most of them can be completely or at least partially relieved of their wheezing and dyspnea. Competent allergy measures consist first of an accurate, painstaking, detective-type of history. Then follow a thorough physical examination, fluoroscopy, with or without x-ray films, and laboratory work, with special emphasis on a search for eosinophilia. Skin tests come next and should first be done by the scratch method, to avoid possible systemic reactions, then by supplementary intradermal skin tests. These skin tests are followed by clinical trials of avoidance and exposure. Offending substances or foods are removed as completely as possible. If important inhalant materials cannot be completely avoided, we inject a series of extracts made from the causative allergens—this process is called hyposensitization (desensitization).

The cases here illustrated happen to be those of individuals who were thought to have bronchial asthma because they wheezed and were short of breath. Anything, of course, which causes partial

obstruction of the tracheobronchial tree can cause these symptoms. Foreign bodies in the lumen, lesions of the wall itself, or tumors or other swellings by pressure from without—any one of these can simulate bronchial asthma. In one sense we can say that these cause "asthma," but we should jealously guard the term "bronchial asthma" to mean the true allergic type which is manifested by wheezing all over both lungs and in which the expiration is usually longer and more difficult than inspiration, and in which there are other findings common to the allergic diseases.

Eosinophilia is usual in allergic conditions, yet its presence is by no means diagnostic of allergy. There were high percentages of eosinophils in the sputum in the patient with the carcinoma of the trachea and in the case of silicosis. Blood eosinophilia is also common in other conditions, notably trichiniasis and other parasitic diseases, as well as in periarteritis nodosa, Loeffler's syndrome, and tropical eosinophilia. Nasal smears, however, are very accurate—a finding of 10 per cent eosinophilia or more is almost always diagnostic of some form of allergic rhinitis.

The literature is full of reports of cases in which the differential diagnosis from bronchial asthma is discussed. Much of this has been summarized by the author in a book on bronchial asthma,[4] and in reviews of the literature;[5-9] also in articles.[10-12]

From these cases it seems almost superfluous to urge all allergists to become better diagnosticians and all internists to learn more about allergy. Each complements the other; both are essential.

SUMMARY

1) "Nonallergic asthma" can occur from any condition in which there is a partial obstruction of the laryngotracheobronchial tree. It can also occur from sudden dilatation of the left ventricle.

2) We have discussed patients whose wheezing and dyspnea were due to (1) a leiomyoma of the trachea, (2) a carcinoma of the carina, (3) a substernal goiter, (4) silicosis of the lungs, (5) acute cardiac dyspnea (cardiac asthma), and (6) bronchiectasis.

3) We urge all allergists to become more proficient as internists, and also suggest that all internists learn enough about allergy so that they can make correct diagnoses and hurry the allergy surveys which are so important in the treatment of true allergic conditions.

RESUMEN

1) "El asma no alérgica" puede ocurrir en cualquier padecimiento en el que hay una obstrucción parcial del arbol bronquial. También puede ocurrir por la repentina dilatación del ventrículo izquierdo.

2) Hemos discutido casos de enfermos en los que hay disnea silbante, debida a: (1) leiomioma de la traquea; (2) carcinoma de la carina; (3) bocio subesternal; (4) silicosis pulmonar; (5) disnea cardiaca aguda (asma cardiaca) y (6) bronquiectasia.

3) Es urgente que los alergistas sean más acabados internistas, y sugerimos que todos los internistas aprendan bastante de la alergia, de modo que puedan hacer diagnósticos correctos y apresurar las investigaciones alérgicas que son tan importantes en el tratamiento de las afecciones alérgicas verdaderas.

RESUME

1) L'asthme "non allergique" peut survenir dans tous les cas où il existe une obstruction partielle de l'arbre laryngo-trachéo-bronchique. Il peut également provenir d'une dilatation soudaine du ventricule gauche.

2) Les auteurs exposent les observations de malades dont les sifflements respiratoires et la dyspnée étaient dus (1) à un leiomyome, (2) à un cancer de la carena, (3) à un goitre rétro-sternal, (4) à une silicose pulmonaire, (5) à une dyspnée aigue d'origine cardiaque, (6) à des dilatations bronchiques.

3) Les auteurs insistent sur la nécessité de voir les spécialistes en allergie devenir plus compétents que les médecins de médecine générale. Ils proposent également que tous les médecins de médecine générale étudient suffisamment la question de l'allergie, pour qu'ils puissent faire le diagnostic correct et proposer les recherches au point de vue de l'allergie, qui sont si importantes quand elle est véritablement en cause.

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Discussion

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Dr. Unger has vividly emphasized Dr. Chevalier Jackson's dictum of "All is not Asthma that Wheezes."

The fact that some of these patients may be treated uselessly for bronchial asthma is not nearly as important as the fact that the underlying cause of the wheezing is being overlooked in patients in whom proper treatment could produce a cure.

As Dr. Unger points out, adrenalin is not the therapy for the hypertensive and arteriosclerotic cardiac who has an attack of dyspnea and wheezing during the night. Nor are antihistaminics the treatment of choice for the patient with tuberculous endobronchitis, or one with a bronchial adenoma merely because these people wheeze.

Dr. Unger states that so-called "non-allergic asthma" is not common, and that 90 per cent of the cases which suggest asthma have real bronchial asthma, and most of these patients can be completely or partially relieved of their wheezing and dyspnea. This may be true in the allergy clinic—but certainly is not our experience in the chest clinic. The majority of our patients with wheezing, usually over 40, are suffering from chronic bronchitis, bronchiectasis and obstructive emphysema. The majority of them were previously treated in the allergy clinic without benefit. At least to us, they have been a challenge, for despite bronchodilators—KI and antibiotics, they have continued to cough, wheeze, and be short of breath.

I would like to add two cases that fall into the category of "Non-Allergic Asthma."

The first case, M.L., was a 30 year old white female whose first pulmonary symptom was wheezing which began in December 1946. This lasted for one month. It recurred in September 1947 after the delivery of her first child. Soon after she sought medical aid and was diagnosed as bronchial asthma.

She continued under treatment until November 1948 when she developed a productive cough and streaking. At that time an x-ray film of the chest was taken which revealed evidence of a lesion suggestive of tuberculous infection of the right upper lobe.

The patient was hospitalized in December 1948, at which time the physical examination revealed some post tussic rales over the right upper lobe and wheezing more marked over the right lung.

A chest x-ray film showed a fibrotic type of infiltration in the right upper lobe with some honeycombing. The small fissure was elevated. Tomagraphic studies failed to reveal definite evidence of cavitation. The sputum contained tubercle bacilli.

The patient received a six weeks course of streptomycin and PAS and

the wheezing disappeared. The sputa became negative on smears and cultures and she was discharged in September 1949.

In December 1949 the wheezing recurred and an x-ray film showed the same fibrotic type of infiltration in the right upper lobe with some honeycombing. She was again placed on streptomycin and again the wheezing disappeared.

In November 1950 she was seen again with a history of wheezing for several months but it had cleared spontaneously. An x-ray film at that time showed evidence of an atelectatic area in the apex of the right lung. A right lateral film suggested that this involved the apical and posterior segments of the right upper lobe. The sputa were positive for tubercle bacilli.

On December 18, 1950, she had right upper lobe lobectomy. The pathological specimen showed numerous areas of ulcerative endobronchitis, tuberculous in nature, in the apical and posterior segments. There was no evidence of active endobronchial disease in the stem bronchus and no cavity was found. There were numerous nodular areas of tuberculous pneumonia. Since the operation there has been no wheezing.

The second case, F.H., was a 61 year old white woman with a history of cough and wheezing for many years. She was hospitalized in 1947 and 1949 with the above complaints,—and chest x-ray films on both admissions were reported as showing evidence of generalized increase of bronchovascular markings with enlargement of the hila and pronounced accentuation of the basal markings. There was evidence of an old tuberculous lesion in the right apex. The diagnoses on both admissions were:

1) Chronic Bronchitis.
2) Pulmonary Emphysema.
3) Possible Bronchiectasis.

Following discharge for the second time, a sputum culture was reported as positive for Friedlander's Group A Bacillus.

The patient was re-admitted to the hospital on February 24, 1951, complaining of cough, productive of yellowish sputum, wheezing and shortness of breath. A chest examination revealed wheezing on both sides, diminished breath sounds and many moist rales.

The x-ray film of the chest showed evidence of some calcific deposits in the right apex and what appeared to be a diffuse fibrosis throughout both lung fields—with more extensive involvement at the bases. Sputa cultures again showed Friedlander's Group A Bacillus.

She was placed on streptomycin and the wheezing disappeared. Cultures of sputum, however, remained positive for tubercle bacilli. Sensitivity studies showed that the organisms were most sensitive to chloromycetin and therapy was switched to this antibiotic.

A new x-ray film showed considerable resolution of the infiltration on both sides.

The sputa became sterile after three weeks of therapy and has remained so.

Thus before one makes a diagnosis of bronchial asthma—regardless of a history of allergy or positive skin tests—one must first rule out other pathology in the tracheo-bronchial tree.

Neurohemodynamics of Pulmonary Edema. I. Autonomic Influence on Pulmonary Vascular Pressures and the Acute Pulmonary Edema State*

A Preliminary Report

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The vast body of experimental data causally relating central nervous system phenomena to the development of acute pulmonary edema has only infrequently been accompanied by appropriate hemodynamic observations. The term "neurogenic pulmonary edema" has been used to cover this general area and usually this concept is associated, in the minds of many, with an increase in the permeability of pulmonary capillaries arising as a direct effect of nerve impulses on those vessels. The authors know of no data in which there has been demonstrated an increase in the rate of transfer of fluid from the pulmonary capillary to the pulmonary extravascular space in the absence of a rise in pulmonary capillary pressure, and wherein nervous impulses have been shown to be a direct causative influence in this phenomenon.

Recently Cameron and De[1,2] in attempting to produce hydrocephalus in the rabbit injected thrombin and fibrinogen into the cisterna magna. This was soon followed by massive, lethal pulmonary edema. The authors felt that an alteration in pulmonary capillary permeability had probably occurred. This interesting phenomena seemed worthy of further analysis and accordingly the following study was undertaken.

Method

Urethane anesthesia, 4 cc. per kilogram of a 25 per cent solution intravenously was used in the 18 rabbits studied. Morphine (4 mg./kilogram), chloralose (48 mg./kilogram) and urethane (480 mg./kilogram) was used in the 62 dogs studied.

A trimethylene thiophanium d-camphor sulfonate (RO 2-2222 has been shown by Randall et al. to block sympathetic ganglia and

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electrical stimulation of the vagi.[3] This agent was used as a ganglionic blocking agent in these experiments.*

Spinal anesthesia was administered by means of a previously placed subarachnoid catheter.[4]

All pressures were recorded electrically through catheters placed on the arterial and venous sides of the pulmonary and systemic circulations by means of electromanometers.[5] Fluoroscopy was used for catheter placement when needed.

Thrombin (0.5 cc.) and fibrinogen (2.0 cc.) were injected through the atlanto-occipital membrane of the rabbit, and 3.0 cc. thrombin and 12 cc. fibrinogen were used in the dog. In the latter the intracisternal injection was frequently made after the atlanto-occipital membrane had been opened widely, thereby preventing an increase of intracisternal pressure.

Isotonic saline infusions, when used, were given with a positive displacement pump to insure identical rates of administration. The "standard" infusion was 10 cc. per kilogram given in one minute.

Aortic flow (cardiac output minus coronary flow) was measured by diverting the aortic stream through the electromagnetic rotameter of Shipley and Crittenden[6,7] and feeding the output into one of the channels of the direct writing recorder so that pressures and flows could be simultaneously registered.

Results

Observation in the Rabbit: All but one of the 18 rabbits receiving intracisternal fibrin developed massive, lethal pulmonary edema, and the majority showed a voluminous outpouring of pink froth and fluid from the tracheotomy tube either a few minutes prior to or just after cessation of the heartbeat.

Arterial hypertension and elevations of left auricular pressure occurred in the four rabbits in which these determinations were made. In the first of these, left auricular pressure rose from 0 to 41 mm. Hg concomitantly with a mean carotid arterial pressure rise from 55 to 150 mm. Hg and a right auricular pressure rise from −2 to 35 mm. Hg. In the second rabbit, left auricular pressure rose from 7 to 40 mm. Hg while mean carotid arterial pressure rose from 100 to 150 mm. Hg (Figure 1). In the third rabbit left auricular pressure rose from 3 to 25 mm. Hg while mean carotid arterial pressure rose from 75 to 130 mm. Hg. In the fourth, left auricular pressure rose from 0 to 15 mm. Hg while carotid arterial pressure rose from 60 to 140 mm. Hg.

When, by virtue of the open chest preparation, it was possible

*RO 2-2222 (Arfonad) was generously supplied through the courtesy of Dr. Elmer L. Sevringhaus of Hoffmann-LaRoche, Inc., Nutley, N. J.

to observe the left auricle, this was seen to increase approximately four to five times in size within 20 to 30 seconds after the intracisternal injection.

The rabbit lungs were examined immediately post-mortem. Figure 1 is representative of what was found. The lungs were markedly edematous and free fluid as well as foam came from the cut surfaces. There were also circumscribed areas of emphysema.

Observations in the Dog: The period directly after the fibrin injection was characterized by a brief bradycardia which was supplanted by a striking tachycardia within 30 seconds. Although the response of vascular pressures was not uniform, more than three-fourths of the dogs subjected to intracisternal fibrin responded with a significant elevation of pulmonary venous pressures. These rose to levels which varied between 20 and 75 mm. Hg with the average response showing a rise of 30 to 40 mm. Hg. This usually occurred within the first 60 to 120 seconds after the injection and was accompanied by a striking arterial hypertension which varied between 225 and 350 mm. Hg mean arterial pressure. In all dogs in which an elevated left auricular pressure occurred, there was a parallel and approximately equivalent rise in pul-

FIGURE 1

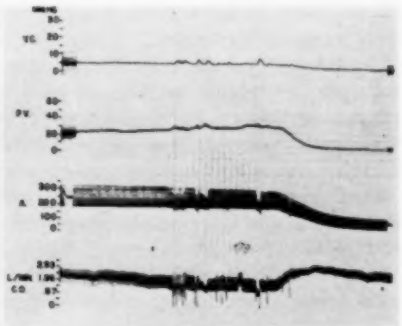

FIGURE 2

Figure 1: Lungs of rabbit No. 3. Died seven minutes after the intracisternal injection of 0.5 cc. thrombin and 2.0 cc. fibrinogen. Pink froth from trachea prior to death.—*Figure 2:* V.C. = vena cava; P.V. = pulmonary vein; A = aorta; C.O. = aortic flow in liters per minute; bottom line = timer (1 second) and signal marker. One hundred gamma protoveratrine were injected intracisternally and bilateral vagotomy was done prior to beginning of tracing. In upper three tracings, solid lines are electrically integrated (mean) pressures. Others are full pulse pressures. At signal, 0.04 mg. per kilogram RO 2-2222 were injected intravenously. (The 3-second elevation of flow at the signal is artefact.) Note rise in aortic flow together with fall in pulmonary venous and aortic pressures after the ganglinoic blockade. There was also a slight fall in vena cava pressure. The pulsus alternans which was present initially disappeared soon after the beginning of diminution in peripheral resistance.

monary arterial pressure. In some dogs a parallel rise of thoracic vena cava pressure of considerable proportions (30 mm. Hg) also occurred but in most instances this was less than 7 mm. Hg.

Effects of Total and Partial Autonomic Blockade on Elevated Pulmonary and Systemic Vascular Pressures: The administration of RO 2-2222 in doses of 0.04 mg./kilogram was followed by a return to control levels of previously elevated pulmonary venous and pulmonary arterial pressures. This occurred in between 30 and 90 seconds after the injection of RO 2-2222. This return to normal levels of pulmonary vascular hypertension was accompanied by a fall in vena caval pressures to or near control values. Concomitant with these changes there was a slight (15 per cent) to pronounced (60 per cent) fall of mean systemic arterial pressures from the excessively high levels that obtained after the intracisternal injection of fibrin. High spinal anesthesia had the same effect as RO 2-2222 but required two to five minutes before the subarachnoid block took effect.

Bilateral mid-cervical vagotomy prior to the intracisternal injection of fibrin did not prevent the development of pulmonary venous and arterial hypertension. When bilateral vagotomy was done after the intracisternal fibrin and the pulmonary vascular hypertension had already developed, these elevated pressures did not fall and in all instances but one rose to somewhat higher (3 to 12 mm. Hg) levels.

The removal of the intact sympathetic chains from the stellate to the fifth thoracic ganglia on both sides prior to the intracisternal injection of fibrin did not prevent the rise of pulmonary or systemic vascular pressures and subsequent bilateral vagotomy at such a time produced a further slight elevation of pulmonary vascular pressures. RO 2-2222 (0.04 mg./kilogram) was then given intravenously and pulmonary venous and arterial pressures fell promptly to the control level.

Effect of Intracisternal Protoveratrine: Of the five dogs in which protoveratrine was injected intracisternally, three had elevations of pulmonary and systemic vascular pressures comparable to that seen with fibrin. The response was not immediate, however, taking about five minutes to develop.

Effect on Aortic Flow of the Intracisternal Injection of Fibrin or Protoveratrine and the Subsequent Administration of RO 2-2222: Aortic flow (cardiac output minus coronary flow) was determined as described above and revealed the following information. Following the intracisternal fibrin and concomitant with the elevation of pulmonary and systemic vascular pressures, there was a fall in aortic flow of between 20 and 40 per cent. This fall in aortic flow began promptly and then reached a low plateau usually one

to two minutes after the peak elevation of pulmonary venous pressure. This occurred in the vagotomized as well as non-vagotomized dog. Subsequently, the administration of RO 2-2222 was followed by a rise in aortic flow concomitant with the fall in pulmonary venous and aortic pressures. The flow rose to an initial peak and then came to a plateau at a level between 30 and 80 per cent above the previous low point (Figure 2).

When a "standard" saline infusion (10 cc. per kilogram in one minute) was given prior to the intracisternal fibrin, there was little or no rise in pulmonary venous pressure, a slight to moderate rise in aortic pressure, and a substantial rise in aortic flow. Contrariwise, in the same dog the same infusion given after intracisternal fibrin was accompanied by a marked further rise in pulmonary venous pressure and little or no rise in aortic pressure and aortic flow. After the subsequent sympathetic blockade, the response to the same infusion was like that seen prior to the intracisternal fibrin.

Effect of RO 2-2222 on Pulsus Alternans: Six of the dogs studied developed left ventricular pulsus alternans during the period of extreme hypertension that followed the intracisternal injection of either fibrin or protoveratrine. In one of these there was a concomitant right ventricular pulsus alternans as well. This occurred in vagotomized as well as non-vagotomized dogs. Sympathetic blockade with RO 2-2222 was followed by the prompt disappearance of the pulsus alternans in each case (Figure 2).

Discussion

Since the response to the intracisternal injection of fibrin is the same when the atlanto-occipital membrane is open as when it is closed, it seems unlikely that alterations in cerebrospinal fluid pressure play a role in this phenomenon. That the fibrin is acting as a non-specific irritant is suggested by the fact that intracisternal protoveratrine may have the same effect.

It is apparent from the data presented above, namely high arterial pressures, low aortic flows and tachycardia, that the intracisternal injection is producing some kind of intense stimulation of the regulatory centers of the cardiovascular system. Beyond this, we have very little understanding of the nature of the local phenomenon.

Deductions concerning the resultant cardiovascular hemodynamic changes that occur are, however, rather more fruitful. The fact that aortic flow falls, while systemic arterial pressure is markedly elevated, makes certain the development of an intense increase in peripheral vascular resistance, in some instances a threefold increase. Inasmuch as this increase in resistance forces

the left ventricle to work at pressures at the upper limit of its functional capacity, the left ventricle, even though presumably normal, may be expected to reach its *work-failure threshold* and be unable to eject all of the blood fed into it by the right heart. This will of course result in an increase of blood in the pulmonary vascular bed and, if this defect persists, in an elevation of pulmonary vascular pressures, among them that in the pulmonary capillary.

Further, systemic vasoconstriction, including the large venous beds, results in a diminution of volume in the peripheral vascular bed. This decrease of blood volume must be volumetrically displaced into some other vascular compartment when the changes are as rapid as those described above. It is more than reasonable to expect that this shift of blood will, under these circumstances, take advantage of a vascular area of very low constrictor potential, namely the lung. The result again is an increase in pulmonary blood volume.

If the pressure-volume characteristics of the vessels of the lung are like those of other vessels, they will tolerate a substantial increase of volume until that point where a further small increase in volume will cause a sharp rise in pressure. It is this state of affairs which, we believe, is brought about by the intracisternal injection of fibrin, namely: 1) an increase in resistance against which the left ventricle is working to a point above its *work-failure threshold* and 2) a significant *shift of blood* from the systemic to the pulmonary vascular bed.

The evidence supporting the increase in peripheral resistance, after intracisternal fibrin, is clear, namely high mean systemic arterial pressures and low aortic flows. That this increase in peripheral resistance is sufficient to exceed the heart's work-failure threshold is suggested by: a) the extent to which aortic flow falls in the presence of markedly elevated left auricular and therefore of left ventricular end-diastolic filling pressures; b) the development of signs of left ventricular strain such as *pulsus alternans;* and c) the fact that the type of infusion, which prior to peripheral vasoconstriction results in an elevation of aortic flow and pressure and no rise in left auricular pressure, after peripheral vasoconstriction, results in a rise in left auricular pressure and little or no rise in aortic flow and pressure.

There can be no doubt that a shift of blood from the periphery to the lung does occur since one can see gross enlargement of the left auricle and engorgement of the pulmonary veins as the pressures therein rise following the intracisternal fibrin.

Evidence supporting the direct participation of the venoconstrictor mechanism in this shift of blood volume is somewhat

more presumptive since left ventricular failure alone could account for it. However, in one experiment where left auricular pressure rose at a point in time *prior* to the elevation of systemic arterial pressure, the most satisfying explanation appeared to be that the venous bed had suddenly poured a large volume of blood into the lung. Further, in those experiments in which systemic venous pressure was markedly elevated, this could not be accounted for solely on the basis of concomitant right ventricular failure.

It would seem from the data presented above that the neuronal pathways responsible for producing these elevated pulmonary vascular pressures are neither in the vagus nor in the sympathetic nerve supply to the lung. For, in the absence of either or both of these pathways, elevated pulmonary vascular pressures still developed after the intracisternal fibrin. On the other hand, when the remaining significant autonomic pathways, namely the sympathetic supply to the peripheral vascular bed, were blocked, pulmonary vascular pressures promptly returned to normal. Further evidence that active pulmonary vasoconstriction itself was not a significant participant in the phenomenon described above is apparent from the fact that the pressure gradient between pulmonary artery and vein increased little, if at all, whereas that between the aorta and vena cava was markedly widened.

From these considerations it is necessary to consider seriously that nervous control of the volume and pressure of the blood in the pulmonary vascular bed is, under certain circumstances, a real and important regulatory mechanism. The pathway for this control, however, is not to be found entirely in the autonomic supply to the lung but rather in those nerves supplying the peripheral vascular bed.

In view of the above findings and their interpretation, it may be tenable to think of treating acute pulmonary edema due to hypertension along the following lines. Peripheral vasodilation, by decreasing the resistance to the left or failing ventricle, will permit the transformation of a larger proportion of cardiac energy, for which there is a limited capacity, into flow. Concomitantly, peripheral vasodilation, by increasing the volume of the peripheral vascular bed, will decrease the volume of blood in the pulmonary vascular bed and therefore decrease the pressures therein. It is probably not desirable to produce a precipitous fall in arterial pressure in hypertensive patients, especially in the presence of significant atherosclerosis. It was therefore reassuring to find that even a slight (15 per cent) fall in mean arterial pressure was accompanied by a return to normal of markedly elevated pulmonary vascular pressures.

It is somewhat less compelling to incriminate the effect of nerve

impulses on pulmonary capillary permeability when it can be demonstrated that pulmonary venous pressure rises to levels adequate to explain the edema that ensues. Accordingly the loose designation "neurogenic pulmonary edema" has been discarded in favor of what authors believe to be a more meaningful term, namely, "neurohemodynamic pulmonary edema."

These experimental studies would seem to explain the therapeutic effect of spinal anesthesia when given to patients in acute pulmonary edema as previously described.[8] It was thought, however, that it would be much more desirable to be able to accomplish a quantitative and readily reversible peripheral vasodilation pharmacologically. Accordingly, an investigation into the action of RO 2-2222 in man was instituted. Preliminary results in the 16 hypertensive patients studied thus far have revealed that it has certain attractive features.[9] More specifically, the dose-response relationship is such as to permit a graded reduction of arterial pressure to whatever levels are desired. Further, the cessation of the intravenous drip containing this drug is followed by a prompt (3 to 15 minute) return of arterial pressure to control levels (Figure 3). Toxicity appears to be low.

The role of the sympathetic pathways in producing pulmonary edema, the changes in pulmonary blood volume, and other hemodynamic sequences in pulmonary edema are described in detail elsewhere.[10-13]

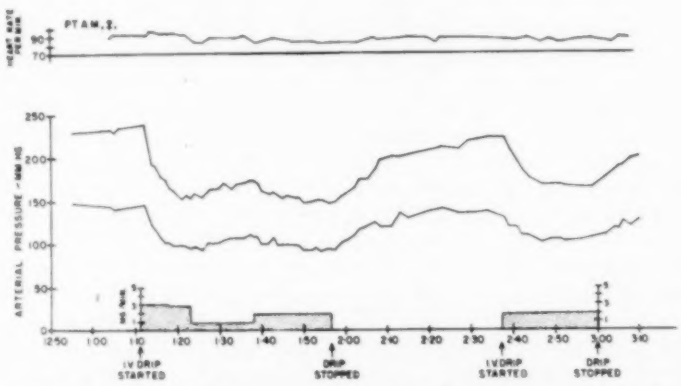

FIGURE 3: Patient A.M. Shows fall in arterial pressure during administration of RO 2-2222. Arterial hypotension approximately proportional to rate of administration. The drug was in a continuous infusion of a solution of 5 per cent dextrose in water containing 2 mg. per cubic centimeter. The drip rate was then adjusted to vary the rate of administration as shown. Arterial pressure rose promptly after cessation of the drip and fell again after restarting it, indicating a lack of tachyphylaxis within this period.

SUMMARY

1) The intracisternal injection of thrombin and fibrinogen produces acute pulmonary edema in the rabbit and dog.

2) The immediate post-injection period is characterized by the development of arterial and venous hypertension in both the pulmonary and systemic circulations, with pulmonary venous pressures that may reach 75 mm. Hg in the dog.

3) This cardiovascular response is also accompanied by a significant decrease in aortic flow.

4) Concomitantly there occurs a grossly observable increase in the size of the left auricle and engorgement of the pulmonary veins providing presumptive evidence of an increase in pulmonary blood volume.

5) In some experiments pulsus alternans occurred during the period of low aortic flow and elevated aortic and pulmonary venous pressures.

6) The elevation of pulmonary and systemic vascular pressures was not prevented either by vagotomy or upper thoracic sympathectomy, nor did vagotomy lower these elevated pressures after they had developed.

7) The administration of sympathetic blockage by either spinal anesthesia or RO 2-2222 was followed by a fall in aortic, vena caval, pulmonary arterial, and pulmonary venous pressures simultaneously with a rise in aortic flow. Pulsus alternans, when it occurred, reverted to normal rhythm soon after sympathetic blockade.

8) It is believed that the intracisternal injection of fibrin, among other things, stimulates cardiovascular centers and that this in turn increases the resistance against which the left ventricle is made to work. This increase in peripheral resistance may then exceed the *work-failure threshold* of the left ventricle resulting in elevated pulmonary vascular pressures.

9) The shift of significant amounts of blood from the peripheral to the pulmonary circulation is probably enhanced by systemic vasoconstriction, since this latter phenomenon decreases the volume of the peripheral vascular bed.

10) Since markedly elevated pulmonary vascular pressures can be returned to normal levels with only a moderate decrease in arterial pressure in hypertensive dogs, it seems reasonable to attempt to treat clinical pulmonary edema in this manner. It is felt that a carefully graded peripheral vasodilation, such as seems to be obtainable with RO 2-2222, would provide the means for: a) decreasing the work of the left ventricle per unit of flow, and b) shifting blood from the pulmonary to the peripheral circulation. Clinical evidence supporting this hypothesis may be found

in the observation that spinal anesthesia confers a therapeutic effect on the acute pulmonary edema state of the hypertensive patient.

RESUMEN

1) La inyección intracisternal de trombina y fibrinógeno produce edema pulmonar agudo en el conejo y en el perro.

2) El período inmediato después de la inyección está caracterizado por desarrollo de hipertensión arterial y venosa, en ambas circulaciones, la pulmonar y la general, con presiones de la vena pulmonar que pueden alcanzar los 75 mm. de mercurio en el perro.

3) Esta respuesta cardio-vascular va también acompañada de una disminución significativa del flujo aórtico.

4) Al mismo tiempo ocurre un aumento fácilmente observable en el tamaño de la aurícula izquierda y un engrosamiento en las venas pulmonares haciendo presumir un aumento del volumen de la sangre pulmonar.

5) En varios experimentos se presentó pulso alternante durante el período de bajo flujo aortico y elevadas presiones aórticas y pulmonares.

6) La elevación de las presiones en vasos pulmonares y en la circulación general no fué evitada por vagotomía, ni por la simpatectomía superior torácica. Tampoco la vagotomía logro bajar estas elevadas presiones después de que se hubieron presentado.

7) La producción del bloqueo simpático por ya sea anestesia espinal ó RO 2-2222, fué seguida de un descenso de las presiones aórtica, de la cava, de la arteria y vena pulmonares, y ocurrió al mismo tiempo un aumento en el flujo aórtico. Cuando ocurrió, el pulso alternante volvió al ritmo normal poco después del bloqueo simpático.

8) Se cree que la inyección intracisternal de fibrina, entre otras cosas, estimula los centros cardio-vasculares y estos aumentan la resistencia contra la cual se hace trabajar al ventrículo izquierdo. Este aumento en la resistencia periférica puede entonces exceder el umbral de la insuficiencia del ventrículo izquierdo, resultando en presiones pulmonares elevadas.

9) El desplazamiento de importantes cantidades de sangre de la circulación periférica a la pulmonar es probablemente aumentado por la constricción sistémica de los vasos, ya que este último fenómeno disminuye el volumen del lecho periférico vascular.

10) Puesto que las presiones de vasos pulmonares elevadas marcadamente pueden ser regresadas a sus nivéles normales con sólo un descenso moderado en la presión arterial de perros hipertensos, parece razonable el tratar edema pulmonar clínico de esta manera. Se cree que una dilatación vascular periférica cuidadosamente

graduada, tal como según parece se puede obtener con RO 2-2222, proporcionaría los medios para: a) disminuir el trabajo del ventrículo izquierdo por unidad de flujo y b) cambiar la sangre de la circulación pulmonar a la periférica. La evidencia clínica para sostener tal hipótesis puede ser encontrada en la observación de que la anestesia espinal confiere un efecto terapéutico en el estado de edema pulmonar agudo del paciente hipertenso.

RESUME

1) L'injection intracisternale de thrombine et de fibrinogène provoque des oedèmes pulmonaires aigus chez le lapin et chez le chien.

2) La phase faisant suite immédiatement à l'injection se caractérise par l'apparition d'une hypertension artérielle et veineuse dans les circulations pulmonaire et systemique. La pression pulmonaire veineuse peut atteindre 75 mm. de mercure chez le chien.

3) Cette réponse cardio-vasculaire est accompagnée par une remarquable diminution du courant aortique.

4) Concuremment on note une augmentation considérable des dimensions de l'oreillette gauche et des veines pulmonaires, ce qui fait prévoir une augmentation du volume sanguin de la circulation pulmonaire.

5) Au cours de quelques expériences, un pouls alternant apparut pendant la période de l'aibaissement de la circulation aortique, et les pressions elevée aortique et pulmonaire veineuse.

6) L'élévation des pressions pulmonaire et systémiques vasculaires du système pulmonaire n'a pu être empêchée, soit par section du pneumogastrique, soit par sympathectomie de la chaine thoracique supérieure. La section du pneumogastrique n'abaissa pas non plus les pressions élevée après qu'elles aient apparu.

7) Le blocage sympathique soit par anesthésie rachidienne, ou par un produit de synthése (RO 2-2222) fut suivi d'une chute de la pression dans l'aorte, la veine cave, l'artère pulmonaire et les veines pulmonaires, tandis que, en même temps, s'élevait le flux aortique. Lorsque survint le pouls alternant, le retour au rythme normal apparut rapidement après le blocage sympathique.

8) Les auteurs pensent que l'injection intracisternale de fibrine, entre autres choses, stimule les centres cardio-vasculaires et finalement augmente la résistance contre laquelle lutte le ventricule gauche. Cette augmentation dans la résistance périphérique peut même dépasser la limite de travail du ventricule gauche, entrainant une élévation des pressions pulmonaires.

9) La poussée de sang désertant la périphérie pour rejoindre la circulation pulmonaire est probablement renforcée par une vaso-

constriction systématique, laquelle abaissa le volume de la circulation systémique.

10) La pression pulmonaire même très élevée peut redevenir normale, avec une diminution très discrète de la pression artérielle chez les chiens hypertendus. Il semble logique de traiter cliniquement l'oedème pulmonaire en mettant à profit cette notion. Une vaso-dilatation périphérique prudente telle que celle qu'on semble obtenir avec le produit RO 2-2222 permettra: a) une diminution du travail du ventricule gauche; b) un déplacement du sang de la circulation pulmonaire vers la circulation périphérique. La preuve clinique de cette hypothèse nous est offerte par le fait que l'anesthésie intrarachidienne a un effet thérapeutique dans l'oedème aigu du poumon dû à l'hypertension artérielle.

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Discussion

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The problem of pulmonary edema is an unusually complex one because of the large number of variable factors always to be considered. In addition to the method used by the Drs. Sarnoff, numerous techniques have been devised to produce pulmonary edema in the experimental animal. These include such diverse methods as the intravenous injection of large quantities of ammonium salts, bilateral cervical vagotomy alone, or in conjunction with intravenous fluids, production of severe injury to the left ventricle, craniad injection of fluids under high pressures into the common carotid arteries, the production of hemorrhagic shock, and the inhalation of noxious gases. The difference in pathogenesis is obvious when one compares the pulmonary edema resulting from aortic arch ligation with that produced by phosgene inhalation. It is when less direct methods are used and compared, that much uncertainty arises about the exact mechanism of production of the edema.

Dr. Sarnoff has suggested that in his experiments, the phenomenon could be explained by the combination of backward failure of the left ventricle and the shifting of much of the blood from the systemic to the pulmonary pool. He correctly indicated that there was no evidence for so-called "neurogenically induced increased capillar permeability" in the lungs. However, since the permeability of a membrane usually bears an inverse relationship to its thickness, it may be seen that once excessive capillary dilation has occurred, some increased permeability may result because of the "thinning out," as it were, of the capillary wall. Furthermore, the oxygen supply of the cells composing the capillary walls in the alveoli is obtained from the alveolar air, and as indicated by Drinker, once a layer of transudate forms over the capillaries and also obstructs many of the bronchioles, anoxia of the capillary walls will develop, and true increased permeability probably results. For this reason the edema fluid first formed may be a transudate with a very low protein content while that produced later and found eventually at necropsy may contain a much higher concentration of protein, as well as many red cells. This difference in protein content of early and late pulmonary edema fluid was observed by the Koenigs in their experiments with ammonium chloride pulmonary edema in the cat and guinea pig. I would like to ask Dr. Sarnoff if measurements were made of the protein content of the edema fluid at various stages of the experiment. Dr. Sarnoff showed very clearly the relationship between the

elevated systemic arterial pressure, left atrial pressure, pulmonary arterial pressure, reduced cardiac output, and thoracic vena caval pressure in the dog. It would be valuable, however, if in addition he would describe the sequence of pressure changes in these various systems, and the usual rapidity of rise or fall of pressures in these systems. I assume from his mention of one case where the atrial pressure rose before the systemic arterial pressure did, that usually the first change was rise in systemic arterial pressure.

How often did pulmonary edema occur in these dogs? Was the difference in incidence of pulmonary edema among the two types of experimental animals merely due to the species variation in cardiovascular response? Dr. Sarnoff stated that slightly less than 25 per cent of the dogs, in spite of intracisternal fibrin injection, did not develop an elevation of pulmonary venous pressure. Did any of these dogs nevertheless develop changes in pulmonary arterial pressures? Did any of these animals in the absence of increased pulmonary venous pressure develop pulmonary edema? As early as 1902 it was learned that pulmonary edema could be produced by the intravenous injection of epinephrine, although the exact mechanism of its production has never been completely explained. Could the intracisternal injection of irritants have led to the release of large amounts of epinephrine, which in this way would have simulated these early experiments.

It would be interesting, also, to know what effect the injection of some of the newer sympatholytic drugs, such as Dibenamine, Benzodioxane, and Dihydroergocornine, would have on the vascular dynamic sequellae of intracisternal injection of fibrin. It might be valuable also to see if other vasodilators such as nitrites or papaverine, by enlarging the systemic vascular pool, would have the same cardiovascular hemodynamic effects on these animals as the thiophanium derivative used. Was it possible to use any of the drugs mentioned to actually prevent or reverse the development of pulmonary edema in either experimental animals?

Finally, it should be stated that two important variables remain which are as yet imperfectly understood. These are (1) the constrictor tone of the pulmonary arterioles and its protective action against overdistension of the pulmonary capillaries, and (2) the exact role of the bronchiolar muscular tone and secretions in the production of inspiratory obstruction.

The Early Recognition of Bronchiogenic Carcinoma*

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Once regarded a pathologic rarity,[1] primary pulmonary malignancy has come to occupy first place among all cancers as a cause of death in men. In spite of the progress that has been made in thoracic surgery, the over-all salvage rate for bronchiogenic carcinoma has remained discouragingly low primarily because this tumor is seldom detected early enough to permit complete extirpation.[2-5]

Some have contended that there are no symptoms or signs that will aid the clinician to recognize early bronchiogenic carcinoma.[6] Others have confessed a lack of specificity of symptoms and roentgenographic changes.[7] All are agreed that there is a silent phase of variable duration, during which the growth causes no symptom, and that some tumors produce symptoms too late to permit early detection.

We believe that there are significant early symptoms and roentgen abnormalities in a high percentage of cases that will suggest a presumptive diagnosis of bronchiogenic carcinoma so that specific methods of diagnosis will be sought. It is our purpose to focus attention on this aspect of cancer detection.

Material

During a four and one-half years' period, we have seen 150 patients with histologically proved bronchiogenic carcinoma. Exploratory thoracotomy was done on 35 per cent of the entire group, but only 12 per cent of the total were suitable for resection. Five of those resected are still living; however, resection was thought possibly curative in only two. These disappointing results prompted a survey of the clinical records which disclosed that avoidable delays in diagnosis had occurred in most instances.

An average of 10.5 months elapsed between the onset of symptoms and the establishment of a correct diagnosis. Delay attributable to the patient averaged 4.1 months and to the physician 6.4

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TABLE I

CLASSIFICATION OF BRONCHIOGENIC CARCINOMA BY LOCATION

Location	*Symptoms*	*Radiographic Findings*	*Bronchoscopy*	*Cytology*
Main stem or lobar bronchi	*Early* 1 Silent for variable period 2 Cough or change in cough 3 Localized wheeze 4 Recurring pulmonary infection 5 Hemoptysis 6 Non-specific	*Early* 1 Unilateral hilar nodularity 2 Localized emphysema on expiration 3 Persistent or recurring infiltration (pneumonitis)	*Early* Frequently positive	*Early* Frequently positive
Segmental bronchi	*Early* 1 Silent for variable period 2 Cough or change in cough 3 Recurring pulmonary infection 4 Hemoptysis	*Early* 1 Segmental infiltration and/or atelectasis 2 Lung abscess distal to bronchial obstruction 3 Filling defect on bronchogram	*Usually late* Occasionally positive early	*Early* Frequently positive
Mid lung peripheral tumors	*Late* 1 Silent for long periods 2 Cough and hemoptysis 3 Hypertrophic pulmonary osteoarthropathy may occur early	*Early* 1 Solitary pulmonary mass or "Coin" lesion (May be detected if 3 mm. in diameter)	*No value*	*Rarely helpful* Becomes positive late
Peripheral invasive tumors	*Late* 1 Onset of pain indicates hopelessly advanced disease 2 Osteoarthropathy may occur early	*Early* 1 Peripheral mass 2 May not be visible until late	*No value*	*No value*

months. The failure of the referring physician to recognize or suspect the presence of primary pulmonary neoplasm at its incipience most commonly resulted from three errors: (1) A lack of awareness that minor respiratory symptoms, particularly in males in the fifth and sixth decades of life, often signal the clinical onset of carcinoma, which led to the second error; (2) failure to obtain a chest roentgenogram early in the course of the disease; and, all too frequently when this study was available, (3) significant departures from normal were either overlooked or misinterpreted.

We propose to correlate the early clinical and radiographic features of bronchiogenic carcinoma with its site of origin within the bronchial tree (Table I). Early manifestations denote abnormalities that are detectable while the growth is still confined to the lung.

Early Clinical and Roentgenographic Features of Carcinomas Arising in Main Stem or Lobar Bronchi:

Fifty-eight per cent of the malignancies in our entire series had their site of origin within the main stem or lobar bronchi. Characteristically, tumors in this location produced symptoms of bronchial irritation, infection or hemorrhage relatively early in their course. The most common early roentgen abnormality on

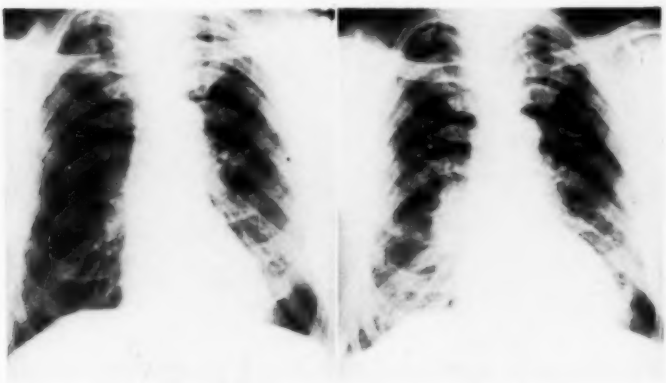

FIGURE 1 FIGURE 1a

Figure 1: Chest roentgenogram on a 62-year-old Negro with complaint of wheezing sensation in right side of chest, interpreted as "Negative." Nodular enlargement of the inferior aspect of the right hilar shadow overlooked.—*Figure 1a:* Mass lesion in the right hilum is more evident on admission film three years later. Bronchoscopy was negative, but exploration confirmed presumptive diagnosis of bronchial carcinoma, squamous cell type. There was no evidence of lymphatic dissemination, but his poor condition precluded resection.

the ordinary inspiration film was a slight, unilateral, easily overlooked, nodular enlargement of the hilar shadow. Occasionally the endobronchial extension of the growth was large enough to give striking signs of bronchial obstruction, manifested by localized wheeze or emphysema. More often the endobronchial portion was small at its onset; hence, complete obstruction of a lobar bronchus, resulting in radiographic evidence of atelectasis, usually portended a well advanced malignancy. Arising close to the hila, they were prone to invade vital mediastinal structures and to extend to the hilar lymph nodes comparatively early. Rarely squamous cell carcinomas were found to be extremely slow growing and to remain localized for long periods. Curative excision generally depended upon a diagnosis in the asymptomatic phase or during the period of minimal symptoms (Figures 1 and 1a).

The most frequently encountered minimal symptoms of major bronchial tumors were cough and recurrent respiratory infection. Unfortunately, cough has become such a common symptom among cigarette smokers that its diagnostic significance has been seriously compromised. Approximately one-third of the patients with tumors in the lobar bronchi had a clinical onset characterized by

FIGURE 2

FIGURE 2a

Figure 2: Admission film on a 29-year-old man with acute pneumonia in base of right lung.—*Figure 2a:* The infiltration cleared during penicillin therapy revealing a mass in the right lower lobe. On bronchoscopic examination a smooth vascular tumor almost completely occluded the right lower lobe bronchus. The presumptive diagnosis was bronchial "adenoma." The tumor measured 4 x 3 x 3 cm. and resided for the most part without the bronchial lumen. The futility of attempting to remove such growths locally via the bronchoscope is graphically illustrated. Histopathologic diagnosis, bronchial adenoma, carcinoid type. Metastasis to a hilar lymph node had occurred. We believe bronchial adenomas behave as cancers, given sufficient time, and should no longer be regarded as benign tumors.

recurring respiratory infection. Their symptoms can be best described by the variety of diagnosis that were made. These included the common cold, bronchitis, grippe, flu, virus, or atypical pneumonia, unresolved pneumonia and tuberculosis. The erroneous diagnoses tended to be confirmed, and a false sense of security was imparted, by the prompt symptomatic improvement that resulted when antibiotics were employed. The cough usually persisted, and the infection recurred after antibiotics were temporarily discontinued. Trials of first one and then another of the antimicrobial agents were administered for weeks and sometimes months. It is absolutely requisite that all acute pneumonic infiltrations be observed until complete radiographic clearing is assured, if errors in early detection are to be avoided (Figures 2 and 2a).

In our experience 25 per cent of all lung abscesses are secondary to bronchial carcinoma.[8] An acute lung abscess should, therefore, be carefully studied to exclude carcinoma, and prompt radiographic improvement should result, before undertaking a prolonged course of antibiotic therapy. If the walls of the abscess appear scalloped, the lesion is most surely carcinoma and should be attacked surgically at once (Figures 3 and 3a).

Roughly one-fourth of the patients with major bronchial tumors had an insidious onset of non-specific complaints, e.g., malaise, fatigue, vague pains and gradual weight loss. Chronic cough and dyspnea were sometimes present but never striking. Not uncom-

FIGURE 3 FIGURE 3a

Figure 3: Chest roentgenogram of a man, aged 55 years, whose primary complaint was hemoptysis. Density is localized to the dorsal segment of the left lower lobe. A tumor mass had been seen bronchoscopically in the left lower lobe bronchus on three occasions elsewhere, but failure to obtain a positive biopsy had resulted in a decision to defer surgery.—*Figure 3a:* Six months later there has been no significant change in the appearance of the lesion as judged by our admission film. After another negative biopsy, the presumptive diagnosis of bronchial carcinoma was confirmed at thoracotomy. The segmental density was due to a cholesterol pneumonia distal to the blocked bronchus.

monly an exacerbation of a chronic illness in another system, such as peptic ulcer, hypertrophic arthritis or cardiac disease were the initial symptoms. Unusually long delays in arriving at the correct diagnosis are apt to occur unless the chest roentgenogram is employed routinely.

Early Clinical and Roentgenographic Features of Carcinomas Arising in the Segmental Bronchi:

The segmental bronchi were the site of origin of 19 per cent of the malignancies comprising the entire study. Arising in bronchi of comparatively small diameter, these tumors were characterized by the early appearance of atelectasis and infection of the distal pulmonary segments. Hemoptysis was likewise a repeated symptom.

Chest roentgenograms were recognized as definitely abnormal readily enough, but as a rule there was nothing characteristic about these segmental densities to distinguish them from tuberculosis when they involved the upper lobes or from pneumonia when they occupied the lower lobes. If antibiotics were employed the symptoms usually improved and partial clearing of the radiographic evidence of infection distal to the tumor commonly resulted. Pneumonitis that fails to completely clear or tends to recur

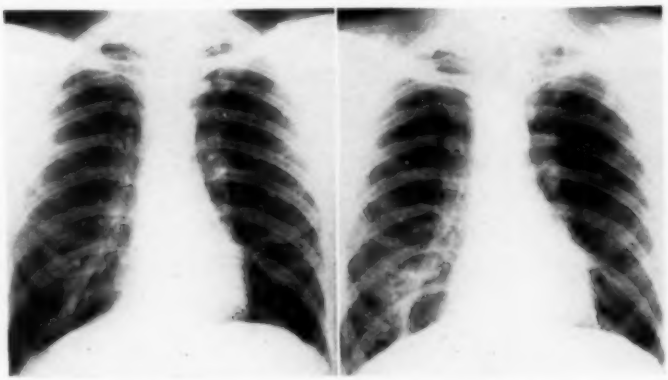

FIGURE 4 FIGURE 4a

Figure 4: Chest roentgenogram of a 49-year-old man with hemoptysis read as "Negative." Shadow in the right lower lobe apparently disregarded.—*Figure 4a:* One year later he returned because of recurring colds and blood streaked sputum, at which time the shadow in the right lower lobe had increased in size and density. Iodized oil failed to enter the posterior basilar segmental bronchus of the right lower lobe. The bronchial mapping was repeated and a filling defect in this bronchus with bronchiectasis distal to the lesion was demonstrated. The bronchial obstruction was produced by a bronchial carcinoma.

in the same pulmonary segment should, therefore, prompt an immediate investigation for bronchiogenic carcinoma.

Bronchograms are an uncertain aid to the early detection of carcinomas involving the segmental bronchi. Occasionally they have been useful in demonstrating an obstruction or filling defect in a segmental or tertiary bronchus (Figures 4 and 4a).

Early Clinical and Roentgenographic Features of Carcinomas Arising in the Periphery of the Bronchial Tree:

Small bronchioles, deep in the parenchyma of the lung, gave rise to 23 per cent of the carcinomas in our entire series. These tumors appeared radiographically as solitary masses, usually sharply circumscribed, and have been referred to as "coin" lesions. Such peripheral carcinomas frequently attained considerable size before producing symptoms. Symptoms eventually developed from extension of the growth to the larger bronchi, if deeply situated; whereas, subpleural tumors invaded the pleura, thoracic cage, adjacent viscera or vertebral bodies and were characterized by intractable pain. Pancoast-Tobias syndrome symbolizes the hopelessly advanced form of a peripheral tumor arising above the superior pulmonary sulcus. Seven such peripheral invasive carcinomas, as they have been referred to by Neuhof and Aufses,[9] occurred in our series.

The early diagnosis of peripheral tumors generally depends on their detection by means of survey chest roentgenograms prior to the onset of symptoms. Adopting a conservative or "wait and see" program in the management of these seemingly innocent shadows may be disastrous. The primary tumor may appear unchanged on the chest roentgenogram for months or years, while extensive blood born metastases have taken place. When confronted with a solitary pulmonary mass, it is frequently impossible to distinguish between a primary malignancy of the lung and a host of other lesions; tuberculoma, mycotic infections, pulmonary cyst, encapsulated lung abscess, metastatic malignancies, and benign tumors to mention a few. More than one-third of such lesions prove to be bronchiogenic carcinoma at exploration (Table II). Given a fair risk patient, if the diagnosis remains in doubt after the application of all diagnostic studies, exploration should be carried out without delay.

Stable lesions containing calcium are the only exception to this rule. We believe such calcified masses to be either tuberculomas or benign tumors and the need for resection may be judged on grounds other than the probability of malignancy.

Occasionally, hypertrophic pulmonary osteoarthropathy may make its appearance during the silent phase of bronchiogenic

carcinoma.[17] An onset of painful swelling of the peripheral joints accompanied with clubbing of the fingers and toes requires that a chest roentgenogram be obtained promptly (Figures 5 and 5a).

A case exemplifying the difficulties encountered in attempting to classify coin lesions clinically is illustrated in Figures 6 and 6a.

The survey chest roentgenogram promises to be one of the most valuable tools available today for the early detection of primary pulmonary malignancy. In contrast to the usual 20 per cent resectability rate[5] and 8 per cent gross five-year survival

TABLE II
ETIOLOGY OF SOLITARY PULMONARY MASSES*

Author	Total Cases	Tuberculosis	Bronchiogenic Carcinoma	Miscellaneous
Thornton et al.[10]	23	4	13	6
Grow et al.[11]	86	37	20	29
O'Brien et al.[12]	21	8	8	5
Effler et al.[13]	24	7	1	16
Johnson et al.[14]	53	3	35	15
Bugden[15]	8	1	3	4
Freedlander et al.[16]	8	2	3	3
Jewett	17	1	9	7
TOTAL	240	63	92	85

*Positively identified at exploratory thoracotomy.

FIGURE 5

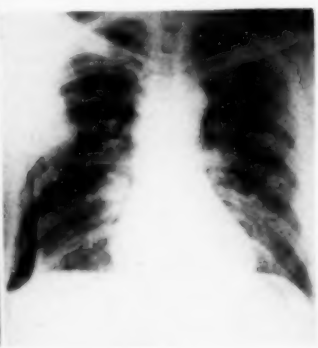

FIGURE 5a

Figure 5: A 40-year-old man sought medical attention because of stiffness and painful swelling of all the peripheral joints. Asymptomatic density in periphery of the right upper lung field was disclosed.—*Figure 5a:* An induced pneumothorax demonstrated pleural symphysis over the mass. At thoracotomy the presumptive diagnosis of peripheral invasive carcinoma was confirmed.

rate,[4] Overholt has reported a 100 per cent resectability rate among a group of patients with asymptomatic bronchial carcinomas detected by survey roentgenograms. Moreover, he regarded 75 per cent of these resections as possibly curative.[18]

Until the public and the medical profession, as well, are apprised of the value of an annual chest roentgenogram, most victims of primary pulmonary malignancy will continue to consult physicians after symptoms have developed. Unfortunately, it is in this group of patients, who require treatment so urgently, in whom the tumor is frequently unsuspected.

There has been no attempt to evaluate the specific methods of diagnosis;[5] but, suffice to say, "The last court of appeal is the surgical amphitheater for the unverified cancer-suspect case."[6]

SUMMARY

We are not in accord with the concept that there are no symptoms or signs that will aid the physician to detect early primary pulmonary malignancy. By correlating the early clinical and radiographic features of a bronchiogenic carcinoma with its site of origin within the bronchial tree, it is hoped that the protean manifestations of this cancer will be better understood. A number of illustrative cases have been briefly reviewed.

RESUMEN

No estamos de acuerdo con el concepto de que no hay síntomas ni signos que ayuden al médico a descubrir un tumor maligno

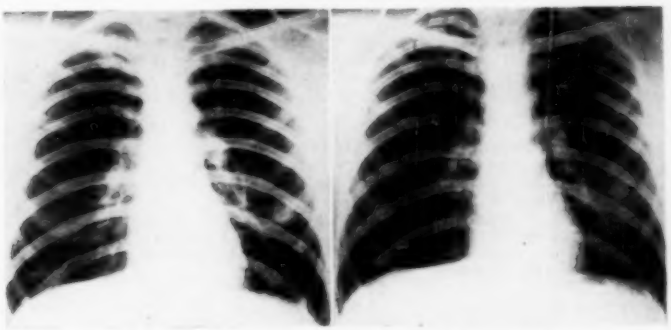

FIGURE 6 FIGURE 6a

Figure 6: "Coin" lesion in left lower lung field discovered on a survey chest roentgenogram. Sputum studies for tubercle bacilli yielded two positive smears and five positive cultures.—*Figure 6a:* No change in the appearance of the lesion occurred over a period of three months during streptomycin and PAS therapy. This lesion proved to be a bronchiogenic carcinoma following lobectomy. Multiple sections were examined, but in none was there evidence of tuberculosis.

primario del pulmón. Maciendo una correlación de las fases clínicas y radiológicas tempranas del carcinoma bronquiogénico con su punto de origen dentro del árbol bronquial, se espera que las primeras manifestaciones sean comprendidas mejor. Un número de casos ilustrativos han sido revisados brevemente.

RESUME

L'auteur s'insurge contre la conception qui veut qu'il n'y ait aucun symptôme et aucun signe qui puisse permettre au médecin de découvrir précocément les tumeurs malignes primitives du poumon. Il estime que les manifestations précoces du cancer seront mieux comprises si no établit une corrélation entre les aspects cliniques et radiographiques du cancer bronchique à son début, et sa situation à l'origine dans l'arbre bronchique. L'auteur résume rapidement quelques observations particulièrement suggestives.

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College Activities

19th ANNUAL MEETING PROGRAM

Physicians who wish to request places on the Annual Meeting Program of the College, to be held in New York City, May 28-31, 1953, should write to the Chairman of the Committee on Scientific Program, Arthur M. Olsen, Mayo Clinic, Rochester, Minnesota.

All requests must be accompanied by an abstract as well as the full title of the paper to be presented.

1953 COLLEGE ESSAY AWARD

The Board of Regents of the American College of Chest Physicians offers a cash prize award of two hundred fifty dollars ($250.00) to be given annually for the best original contribution, preferably by a young investigator, on any phase relating to chest disease.

The prize is open to contestants of other countries as well as those residing in the United States. The winning contribution will be selected by a board of impartial judges and the award, together with a certificate of merit, will be made at the forthcoming annual meeting of the College, to be held in New York City, May 28-31, 1953. Second and Third prize certificates will also be awarded.

All manuscripts submitted become the property of the American College of Chest Physicians and will be referred to the Editorial Board of the College journal, "Diseases of the Chest," for consideration. The College reserves the right to invite the winner to present his contribution at the annual meeting. Contestants are advised to study the format of "Diseases of the Chest" as to length, form and arrangement of illustrations, to guide them in the preparation of the manuscript.

The following conditions must be observed:

(1) Five copies of the manuscript, typewritten in English, should be submitted to the executive office, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois, not later than March 15, 1953.

(2) The only means of identification of the author or authors shall be a motto or other device on the title page, and a sealed envelope bearing the same motto on the outside, enclosing the name of the author or authors.

ILLINOIS CHAPTER

A meeting of the Illinois Chapter was held in Chicago, October 9, in conjunction with the 7th Annual Postgraduate Course on Diseases of the Chest. Dr. Theodore J. Wachowski was moderator of the Clinical Pathological X-Ray Conference of the Chapter.

A joint meeting of the Illinois Chapter of the College, the Macon County Medical Society, and the Illinois Trudeau Society was held on November 14, at the Decatur Club, Decatur, Illinois. The scientific program included the following papers:

"When is an Intrathoracic Case a Surgical Problem?"
Robert Fox, Surgical Department, Municipal Tuberculosis Sanitarium, Chicago.

"Recognition and Treatment of Acute Chest Emergencies,"
Paul A. Alfano, Associate Thoracic Surgeon, Cook County Hospital, Chicago.

"Problems Encountered in the Diagnosis of Chronic Chest Diseases,"
Robert H. Ebert, Associate Professor of Medicine, University of Chicago Medical School.

A meeting of the Illinois Chapter will be held on December 12 at the Congress Hotel, Chicago.

Officers of the chapter are as follows:

William J. Bryan, Rockford, President
Abel Froman, Chicago, Vice-President
Clifton F. Hall, Springfield, Secretary-Treasurer
George W. Holmes, Chicago, Chairman, Program Committee.

119th MEETING OF THE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

The 119th Meeting of the American Association for the Advancement of Science will be held December 27 in Kiel Assembly Hall 3, St. Louis, Missouri.

A symposium on "Chemotherapy of Tuberculosis" will be presided over by Dr. Alfred Goldman, Washington University School of Medicine. The following papers will be presented:

"Antimicrobial Therapy of Pulmonary Tuberculosis,"
Forrest W. Pitts, Capt., MC, USA and Carl W. Tempel, Col., MC, USA, Fitzsimmons Army Hospital, Denver, Colorado.

"The Laboratory Evaluation of the Anti-tubercular Activity of the Hydrazine Derivatives of Isonicotinic Acid,"
E. Grunberg, Hoffman-LaRoche, Inc., Nutley, New Jersey and Department of Health, Newark, New Jersey.

"The Acute Pharmacology in Man of the INH Compounds,"
Carl C. Pfeiffer, University of Illinois School of Medicine, Chicago, Illinois.

"Use of Isoniazid and Iproniazid Compounds in Clinical Tuberculosis,"
M. R. Lichtenstein, University of Illinois School of Medicine and Municipal Tuberculosis Sanitarium of Chicago, Illinois.

College News Notes

Dr. Alfred S. Dooneief, Bedford Hills, New York, has recently been appointed attending physician, Division of Pulmonary Diseases, Montefiore Hospital, New York. Dr. Dooneief is the Secretary of the New York Postgraduate Committee of the College.

Dr. Frederick R. Harper of the University of Colorado School of Medicine, Denver, Colorado, was promoted to clinical professor of thoracic surgery and head of the Division of Thoracic Surgery. Dr. Harper is a member of the Council on Postgraduate Medical Education of the College.

Dr. John S. Bouslog of the University of Colorado School of Medicine, Denver, Colorado, has been promoted to clinical professor of radiology. He is a member of the Board of Examiners of the College.

Dr. I. J. Selikoff of Paterson, New Jersey and Dr. Paul K. Bornstein of Asbury Park, New Jersey presented a paper entitled "Isoniazid Derivatives in the Treatment of Tuberculosis" before the Regional Meeting of the American College of Physicians in Newark, New Jersey, on Nov. 5.

Book Reviews

Chest Surgery for Nurses. By J. Leigh Collins and L. E. Mabbitt. Bailliere, Tindall and Cox, London, 1951, 188 pages, $3.00.

This Text Book is characterized by its understandable presentation of its subject matter and by the expressive line drawings which go far in the explanation of the particular subject at hand.

There is a generous discussion of the fundamentals of the basic sciences of anatomy and physiology without the introduction of burdensome and unnecessary details.

The chapters on general clinical principles stresses the fundamentals for the care of patients requiring surgical intervention in the chest.

The chapters dealing with breathing exercises and anesthesia might be used as a quick reference by many medical men.

The chapters dealing with the various diseases and injuries and the surgical measures applicable in their treatment are somewhat general in their presentation of the subject matter but present sufficient understandable information to enable the nurse to care for her patient with some knowledge of the diagnostic and surgical principles involved in the care and management of such patients.

Throughout this book the authors make good use of line drawings to enhance the explanation of various relationships, positions, conditions and instrumentarium. I can recommend this book for the student nurse.

William A. Hudson.

Anesthesia for Thoracic Surgery. By Henry K. Beecher, M.D., Charles C. Thomas, Springfield, Illinois. 65 pages. $2.50.

This concisely written, brief monograph deals with the principles, problems, and practices of anesthesia for thoracic surgery. It is divided into the lobectomy-pneumonectomy group cases with a discussion of the problems, equipment, techniques, etc., of this group of cases. There is also a section on the anesthetic agents and techniques in general for thoracic surgery. It deals also with problems of the termination of the surgery-anesthetic procedures. The latter part of the book deals with special problems with infants and children, cardiac and large vessel surgery, thymectomy, transthoracic esophagectomy, thoracoplasty, etc.

It is obvious that in a monograph so small as this one only the more important factors of each of these problems can be discussed and then only briefly. It is refreshingly, clearly written, giving Dr. Beecher's views on these various problems with reference to Dr. Beecher's numerous papers on the subject at hand.

This monograph presents the views of Dr. Beecher and is designed for the surgeon, internist, student and anesthetist who would desire to have his views of the problem. It accomplishes this purpose and well, and can therefore be recommended. It thus gives one the views of an outstanding group but gives very little, if any, of the views of other outstanding groups, this being justifiable in so short a text.

Max S. Sadove.

Causes and Prevention of Tuberculosis. By Brice R. Clarke, M.D., The Williams and Wilkins Company, Baltimore. 288 pages. $6.50.

This volume, by an authority in Northern Ireland, examines the causes of tuberculosis in great detail. The influence of race, heredity, food, and other environmental factors are carefully analyzed. Numerous charts and graphs are presented to compare the findings in various parts of the world. The work of many writers in this field is quoted and critically examined. The conclusions are clear and logical.

Chapters on epidemiology, the bovine bacillus, and the principles of prevention are well written and informative.

The chapter on mass miniature radiography gives the broad outlines concerning the usefulness of this method, and many helpful suggestions regarding its application.

The chapter on immunization against tuberculosis gives a favorable, but not over-enthusiastic point of view concerning the usefulness of B.C.G.

There is also a brief chapter on the prevention of disease in the infected person, and a chapter on the treatment and rehabilitation of the tuberculous patient.

The medical writing in this volume is clear and easily followed. The conclusions drawn from the wealth of material presented are sound and practical. This book has much that will interest the lay worker in tuberculosis as well as the physicians and nurses in this field.

M. R. Lichtenstein.

ANNOUNCEMENTS

Effective with January 1953 and subsequent issues of *Diseases of the Chest*, the annual subscription rate will be $12.50. The price includes postage to any part of the world.

Due to the increase in printing and mailing costs the Editorial Board of the journal has been obliged to increase the annual price of the subscription.

A Postgraduate Course on Diseases of the Chest for General Practitioners sponsored by Marquette University School of Medicine, the Wisconsin Chapter of the American Academy of General Practice, and the Wisconsin Chapter and the Council on Postgraduate Medical Education of the American College of Chest Physicians, will be held at Marquette University School of Medicine, Milwaukee, Wisconsin, March 4, 11, 18 and 25, 1953, from 1:00 p.m. to 5:00 p.m. The fee will be $25.00. This is an accredited course approved towards postgraduate education requirements of the Wisconsin Chapter of the American Academy of General Practice.

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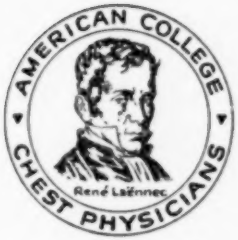

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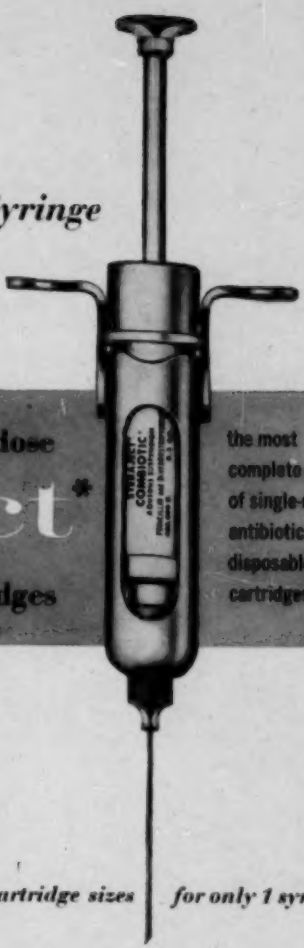


sterile, single-dose

Steraject*

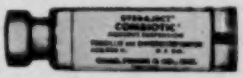
disposable cartridges

the most complete line of single-dose antibiotic disposable cartridges

Steraject Penicillin G Procaine Crystalline in Aqueous Suspension (300,000 units)

Steraject Penicillin G Procaine Crystalline in Aqueous Suspension (1,000,000 units)

Steraject Combiotic* Aqueous Suspension (400,000 units Penicillin G Procaine Crystalline, 0.5 Gm. Dihydrostreptomycin)



Steraject Dihydrostreptomycin Sulfate Solution (1 gram)

Steraject Streptomycin Sulfate Solution (1 gram)

2 cartridge sizes *for only 1 syringe!*

two cartridge sizes permit *full standard* antibiotic dosage

cartridges individually labeled

ready for immediate use

no reconstitution

for full details, ask your Pfizer Professional Service Representative

Steraject Cartridges:
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introduced by Pfizer *world's largest producer of antibiotics*

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